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Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD) (Review)

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TABLE OF CONTENTS

[Intervention Review]

Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD)

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ABSTRACT

Background

Obsessive compulsive disorder is a common and disabling disorder. A significant proportion of patients manifest a chronic course. Individual randomised controlled trials (RCTs) have shown that selective serotonin re-uptake inhibitors (SSRIs) are effective in this condition. Previous systematic reviews or meta-analyses summarising the evidence are methodologically problematic or limited in the scope of their analysis.

Objectives

To examine the efficacy and adverse effects of serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD) in adults.

Search methods

CCDANCTR-Studies and CCDANCTR-References were searched on 12/11/2007. Reference lists were checked. Experts in the field were contacted.

Selection criteria

All RCTs and quasi-RCTs examining the efficacy of SSRIs compared with placebo for OCD in adults were eligible for inclusion.

Data collection and analysis

Selection of studies and data extraction were carried out by two review authors independently, and quality assessment of studies was undertaken. Data analysis was conducted using Review Manager software. Summary measures were produced using the weighted mean difference (WMD) for continuous data and relative risk (RR) for dichotomous data, with 95% confidence intervals (CI). SSRIs were examined as an overall group of drugs, and as individual drugs.

Main results

Seventeen studies were included in the review, involving 3097 participants. Based on all 17 studies, SSRIs as a group were more effective than placebo in reducing the symptoms of OCD between 6 and 13 weeks post-treatment, measured using the Yale-Brown Obsessive Compulsive Scale (YBOCS) (WMD -3.21, 95% CI -3.84 to -2.57). The WMD for individual SSRI drugs were similar and not statistically different. Based on 13 studies (2697 participants), SSRIs were more effective than placebo in achieving clinical response at post-treatment (RR 1.84,

95% CI 1.56 to 2.17). The pooled RR was shown to be similar between individual SSRI drugs. Although reported adverse effects data were more limited, with few exceptions, the overall and individual adverse effects for the different SSRIs were always worse than for placebo and, in the majority of cases, the difference was statistically significant. Nausea, headache and insomnia were always reported amongst the most common adverse effects in trials of each of the drugs.

Authors' conclusions

SSRIs are more effective than placebo for OCD, at least in the short-term, although there are differences between the adverse effects of individual SSRI drugs. The longer term efficacy and tolerability of different SSRI drugs for OCD has yet to be established.

PLAIN LANGUAGE SUMMARY

Selective serotonin re-uptake inhibitors (SSRIs) versus placebo for obsessive compulsive disorder (OCD)

Obsessive compulsive disorder (OCD) is a common and disabling disorder, which frequently follows a chronic course. It is characterised by intrusive thoughts of imagined harm, which are difficult to dispel, and ritualistic behaviour such as repetitive washing of hands and repetitive checking for risk of harm. Individual randomised controlled trials have demonstrated that antidepressants are effective for OCD. This review summarises all the available evidence for one class of antidepressant drugs, the selective serotonin re-uptake inhibitors (SSRIs) (including citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) compared to placebo in the treatment of OCD in adults. The review included 17 studies (3097 participants), and showed that SSRIs were effective in reducing the symptoms of OCD. Based on 13 studies (2697 participants), the review showed that people receiving SSRIs were nearly twice as likely as those receiving placebo to achieve clinical response (defined as a 25% or more reduction in symptoms). Indirect comparisons of effectiveness suggested that although individual SSRI drugs were similar in their effectiveness, they differed in terms of their adverse effects. The most common adverse effect reported by participants was nausea. Further studies involving head to head comparisons between different SSRI drugs are required to obtain more reliable information on differences between SSRIs, both in terms of effectiveness and adverse effects.

BACKGROUND

Description of condition

Obsessive compulsive disorder (OCD) is characterised by obsessions and compulsions. Obsessions are recurrent intrusive and unwanted thoughts that the sufferer cannot dispel. Common themes of the obsessional thoughts include thoughts that the person may cause harm to others or that harm may befall others, or thoughts that the person or others are contaminated. Other common themes of obsessional thoughts are centred on the need for order, symmetry or perfection. The obsessional thoughts are associated with negative affect, usually anxiety, but other emotions such as disgust, guilt or shame may also be experienced. As a response to the feelings generated by the obsessional thoughts, the person may perform compulsions, and performance of the compulsions temporarily decreases the negative affect. The compulsions are stereotypic, ritualised behaviours that are usually observable but which may include covert mental rituals. Common overt rituals include repetitive checking, washing or cleaning, or repetitive rearranging and ordering of objects. Examples of covert mental rituals include repetitive counting, praying or thinking magical statements (Gelder 2001).

Obsessive compulsive disorder is one of the most disabling of anxiety disorders. The obsessions and compulsions may occupy many hours of the person's day and cause severe distress and disruption to the person's life (Rasmussen 1989), as well as disruption to their families (Chakrabarti 1993).

Recent community-based epidemiological studies have shown that the prevalence of OCD is much higher than previous reports based on clinical samples. The cross-sectional prevalence of OCD in the UK was 1% in males and 1.5% in females according to a national survey carried out in 1993 of psychiatric morbidity based on interviews with a nationally representative sample of approximately 10000 people living in private households (Bebbington 1998). In the USA, the lifetime prevalence of OCD was found to be between 1.9% and 3.3% based on the epidemiological catchment area (ECA) study carried out in 1984 of a representative sample of 18500 people from five geographical areas (Karno 1988). In a cross national study carried out using methodology similar to ECA study, lifetime prevalence was found to be 3% in Canada, 3.1% in Puerto Rico, 0.3 to .9% in Taiwan and 2.2% in New Zealand (Bebbington 1998).

Follow-up studies suggest varied outcome. A one year prospective study of 101 patients showed an episodic course in 46% and a chronic course in 54% of patients (Ravizza 1997). Another follow up study of 144 patients, with a mean follow up of 47 years, showed complete remission in 20% and partial improvement in 63% of participants. It also showed that episodic course was common during first 1-9 years and that chronic course was common in the later years (Skoog 1999). A 2-year prospective study of 65 patients showed complete remission in 12% and partial remission in 47% of patients (Eisen 1999).

Aetiology of OCD is uncertain. However current hypotheses for aetiology relate to the possible role of genetic, biological, behavioural and cognitive factors. Although controlled family and twin studies provide some support for the genetic hypothesis, it still remains tentative because the results of studies are inconsistent and in some studies there is no evidence for specific inheritance of OCD (Alsobrook 1998). This may however suggest that OCD is a heterogeneous condition. The evidence that only serotonin reuptake inhibitor (SRI) antidepressants (and not other antidepressants) are effective in OCD led to the development of serotonergic hypothesis (Barr 1993), which although plausible but has not been proven conclusively. The hypothesis suggests that there is some abnormality (presumably a reduction of function) of serotonergic system in OCD or that serotonergic system is implicated in some way in the pathophysiology of OCD. However, the results from studies of peripheral receptor binding in blood and of the relevant metabolites levels in CSF employing comparisons with control values are inconsistent (Rauch 1998a). Furthermore, serotonin depletion studies do not result in reversal of anti-obsessional drug action or exacerbation of OCD symptoms as would be predicted by the hypothesis (Delgado 1998). Thus, it would appear that serotonin plays some part in the disorder, but that perhaps its role may not be primary, but secondary and modulatory. Neuroimaging studies using cross-sectional controlled and pre and post-intervention designs suggest abnormalities of orbito-frontal region and basal ganglia (Saxena 1998, Rauch 1998b). The evidence for behavioural (Baer 1998) and cognitive factors (Steketee 1998) is mainly indirect and is based on the observations that specific behavioural and cognitive interventions have been found to be effective in OCD.

Description of intervention

Over the last few decades, a number of treatment strategies have been developed for most anxiety disorders, including OCD, and tested in randomised controlled trials (RCTs). For OCD, a widely used and effective psychological treatment strategy is behavioural therapy, which consists of exposure-in-vivo coupled with response prevention (Soomro 2003). Some patients may find difficult to engage in behavioural therapy because of the intense anxiety experienced in carrying it out. Unfortunately about 25% of patients offered this form of treatment refuse it, and of those who do accept, 10-20% make minimal gains. Drug treatment with antidepressants may offer help to some of these patients, and also to other OCD patients as a treatment of first choice.

Evidence from individual RCTs shows that serotonin reuptake inhibitors are effective in OCD. Serotonin reuptake inhibitors include non-selective and selective serotonin reuptake inhibitors (SSRIs), an example of the former being clomipramine, and of the latter being citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline.

Why it is important to do this review

Of twelve previously published systematic reviews or meta-analyses on SSRIs for OCD (see Table 1 for summary), eight have serious methodological problems (QAP 1985, Christensen 1987, Jenike 1990d, Jenike 1990c, Cox 1993, van Balkom 1994, Greist 1995, Stein 1995) in that they have used inadequate literature search strategies, have used inappropriate study selection criteria, and/ or when using mixed study designs, did not report separate or adjusted results for RCTs. Although three further reviews (Piccinelli 1995, Abramowitz 1997, Kobak 1998) were free from these serious flaws, they showed other significant problems, including absence of heterogeneity investigation, using fixed effects models in presence of significant statistical heterogeneity and/or not weighting studies according to sample size. None of these eleven reviews explicitly assessed and or explored the methodological quality of the studies used. The twelfth review (Ackerman 2002) is methodologically sound, however, it did not carry out responder

and adverse effects analysis. Furthermore, in relation to sertraline, its analysis was inadequate in the sense that it only analysed this drug versus placebo at a lower dose of 50mg, with findings indicating that it was not superior to placebo, although other RCT evidence has shown sertraline at higher doses to be effective versus placebo. The current review aimed to provide a comprehensive, updating summary and meta-analysis on the effectiveness and adverse effects of SSRIs for OCD.

OBJECTIVES

1) To identify and systematically review evidence of effectiveness of SSRIs in obsessive compulsive disorder in patients of adult age in comparison to placebo
2) To estimate summary effect sizes (pooled relative risk and weighted or standardised mean differences as appropriate) of the treatments if appropriate
3) To carry out an assessment of relationship between effect sizes and methodological features of the studies and demographic and clinical features of patients and treatment characteristics
4) To systematically review and pool data on adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

All trials described as randomised controlled trials (RCTs) or quasi-randomised trials of SSRIs versus placebo in obsessive compulsive disorder were considered for inclusion in the review, including cross-over trials if the relevant data were available for the trial period before the point of cross-over (post-cross-over data would not be appropriate because there would be a carryover effect of active drug from pre- to post-cross-over phase). Quasi-randomised trials are those where allocation sequence is generated by rules that are not truly random, such as allocation by date of birth, day of the week, medical record number etc. There is greater likelihood of allocation not being adequately concealed in these trials, leading to selection bias.

Both published and unpublished studies were considered for inclusion, as there is evidence of publication bias in favour of studies with positive results (Dickersin 1992; Easterbrook 1991; Scherer 1994), therefore, ignoring unpublished studies could introduce bias into a systematic review. Studies were not excluded on the basis of sample size or duration of follow up.

Types of participants

RCTs investigating adult patients (aged 18 years and above) of either sex and any cultural background suffering with OCD were considered for inclusion in the review.

Any commonly accepted diagnostic criteria for OCD were considered eligible, such as International Classification of Diseases, 9th or 10th edition (WHO 1992) or Diagnostic and Statistical Manual of Mental Disorders (DSM), editions III, IIII-R or IV (APA 1994) or some other accepted /standardised criteria. Studies involving patients with other DSM Axis I disorders were excluded, with the exception of secondary depression.

Types of interventions

The intervention of interest was selective serotonin re-uptake inhibitors (SSRIs), at any dose and regimen. The SSRIs include fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram. Only comparisons with placebo were considered. Only those studies where SSRIs were a stand-alone intervention were considered eligible.

RCTs in which SSRIs were used in combination with some other treatment, and which did not allow direct comparison of SSRIs with placebo (i.e. confounded RCTs) were not eligible for inclusion. However, if such RCTs allowed comparison of SSRIs versus placebo, they were considered conceptually eligible for the question of this review. Such trials are likely to show lower (than the true) effectiveness of SSRIs versus placebo, and should not be combined in meta-analysis of trials which used one intervention per arm. However, these trials could be managed as a separate subset within the review, and may be considered for a future update of this review.

Types of outcome measures

Primary outcome

The primary outcome was:
1) Symptomatic improvement measured as a continuous outcome through reduction in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores (Goodman 1989a; Kim 1990). Measurement of outcomes was considered in terms of change differences. Where change data for these were not available or calculable, then end point differences were considered.
2) Response rate as a dichotomous outcome, defined as 25% or more reduction in YBOCS (a common cut off point used in trials)
It was expected that most trials would use YBOCS, as it is most widely used observer rated severity scale in OCD research and has been investigated for validity and reliability. Range of YBOCS is 0 to 40 (higher score representing more severe symptoms). However, if YBOCS was not used by a trial, then it was decided that some other objective instrument of acceptable reliability and validity would be used. Other observer rated but mainly symptom-related instruments used for obsessive compulsive disorder are Psychopathological Rating Scale (PRS) and Symptom Checklist List 90 (SCL 90) (APA 2000; Goodman 1998).

Secondary outcomes

1) Global assessment of severity of OCD symptoms was used as the main secondary outcome of interest. Scales measuring severity in this way are National Institute of Mental Health Obsessive Compulsive scale (NIMH-OCS), the Clinical Global Impression (CGI) scale for severity and the Clinical Global Impression (CGI) scale for improvement (APA 2000). It was also decided that self-rated instruments would be considered as secondary measures if used by the majority of the trials. Examples of self-rated instruments are Maudsley Obsessional-Compulsive Inventory (MOCI) (Hodgson 1977) and Padua Inventory (Goodman 1998).

Other secondary outcome measures considered were:
2) Proportion of patients discontinuing treatment (20% or less discontinuers in a trial versus more than 20%)
3) Adverse events, including overall adverse events, sexual adverse events and three most common adverse events (sexual side effects were considered separately, as these are often a source of great distress to patients, with impact on quality of life and relationships)
4) Social and occupational functioning

5) Quality of life
6) Proportion of relapses (in long term trials)

Depression is usually assessed in OCD research for inclusion criteria, and sometimes as a secondary outcome. Commonly used instruments for measuring depression are the Hamilton Depression Scale (Hamilton 1967, Hamilton 1969), Montgomery Asberg Depression rating scale (APA 2000) and the Beck Depression Inventory (Beck 1961). This review did not use change in depression as a secondary outcome, however the information on measurement of depression was used to sub-group trials on the basis of presence or absence of severe secondary depression.

If a study met the inclusion criteria but did not give the data necessary for estimating effect size, and such data were not available from the authors, then it was decided that the study would be excluded from the analysis, but would be commented upon critically and listed as eligible without usable data for meta-analyses (Petitti 1994)

Search methods for identification of studies

Electronic searches

CCDANCTR-Studies - searched on 12/11/2007
Diagnosis = "Obsessive-Compulsive"
and
Intervention = "Selective Serotonin Reuptake Inhibitors" or Alaproclate or Citalopram or Escitalopram or Femoxetine or Fluoxetine or Fluvoxamine or Paroxetine or Sertraline
and
Intervention = placebo*
and
Age-group = Adult

CCDANCTR-References - searched on 12/11/2007
Keyword = Obsess* or Compulsi*"
and
Free-text = "Selective Serotonin Reuptake Inhibitors" or Alaproclate or Citalopram or Escitalopram or Femoxetine or Fluoxetine or Fluvoxamine or Paroxetine or Sertraline

Reference Lists

Reference lists of the selected studies and previous systematic reviews were searched.

Personal communication

Two active researchers in the area of OCD were contacted personally and asked whether they knew of any unpublished or additional published studies on SSRIs versus placebo in OCD.

Data collection and analysis

Selection of studies

Selection of studies was carried out by two review authors independently for reliability. The selection criteria for inclusion of studies in the review were as follows.
1) The population studied were adults with OCD without co-morbidity of DSM Axis I disorders (except secondary depression)
2) The studies were RCTs, quasi-randomised trials or cross-over trials
3) The intervention used was selective serotonin re-uptake inhibitors (SSRIs)
4) The control group was placebo

Data extraction

Data extraction from the selected studies was carried out by two review authors for reliability. Any disagreements were resolved by discussion (and if necessary through arbitration with a third review author). A specially designed form was used by the reviewers to collect data on methods/quality, participants, intervention and outcome measurements and other relevant features of the trials. The form was piloted by the two reviewers first before data extraction.

Quality assessment

There is some empirical evidence of effect of quality features on trial outcome (Moher 1999). There are also logical reasons for suspecting such a relationship. Two of the components for which there is empirical evidence of such an effect are concealment of allocation and double-blinding. Their lack results in exaggeration of effect of size of trials (Juni 2001). Thus, it is important to assess quality of studies selected for a systematic review and to use it appropriately to minimise bias in the review. It has been suggested that quality should be used for selecting studies and for sensitivity analysis to investigate how robust the results of a review are to different quality features of the studies. It is not recommended that quality assessment be used for weighting studies as there is no empirical evidence for such approach (Juni 2001). Consistent with this approach it has been suggested that quality assessment instruments should not be used as scales with final summation score for the whole scale but as checklists to assess presence or absence of different components of quality (Juni 2001). Thus, quality assessment for this review was used for selection of studies and for sensitivity analysis, that is randomised and quasi RCTs were selected (and non-randomised studies were not selected) and a sensitivity analysis was carried out for quality features where data was available.

The checklist for the four quality components (i.e. selection, performance, detection and attrition bias) was developed using Cochrane Reviewers' Handbook 4.1.1 (Clarke 2002), the revised CONSORT statement (Moher 2001) and other sources (Juni 2001). This quality assessment checklist was pilot tested by the two review authors before use with the trials.

Statistical analysis

Review Manager software was used for data management and relevant statistical analysis for this systematic review. Statistical issues are discussed below in relation to outcome measures, heterogeneity assessment, subgroup and sensitivity analysis, meta-analysis and publication bias.

Dealing with missing data

Continuous/interval data

The data required for meta-analysis of continuous data were mean and SD of change from baseline for each treatment group. For some trials only mean and SD of final values could be extracted. Such studies can be pooled with those reporting change from baseline, as they are estimating the same treatment effect. The following assessments were carried out and/or precautions observed while collecting these data and other relevant information.
1) Efforts were made to spot whether standard error was presented as SD (this mistake is sometimes seen in trial reports).
2) In the case of missing SD, SE or CI, other statistics were used to calculate SD e.g. t or F statistic.
3) Where possible, intention to treat analysis data (where relevant, using last observation carried forward [LOCF] data) and completer

sample data were extracted separately. Information on the number of discontinuers was also extracted for each group.

Dichotomous data
The data required for the meta-analysis of binary data are number of events in each group and total patients in each group. Precautions were taken to extract intention to treat analysis data (last observation carried forward data [LOCF]) separately and completer sample data separately. Information on the number of discontinuers was also extracted for each group.

Measures of treatment effect
For dichotomous data, relative risk (RR) was calculated. The choice of RR instead of odds ratio was mainly based on ease of interpretation. For continuous data, weighted mean difference (WMD) was calculated if the studies used the same scale, however, if they used different scales, the standardised mean difference (SMD) was calculated. These effect sizes (RR, WMD and SMD) were meta-analysed as pooled summary effect sizes (Petitti 1994, Deeks 2001). 95% confidence intervals were also calculated.

To estimate the summary effect sizes, both fixed effects and random effects models were used with RR, WMD and SMD. In absence of clinical and statistical heterogeneity, the fixed effects model would serve as the model of choice, and random effects model would serve to check the robustness of the fixed effects model. However, in the presence of either clinical or statistical heterogeneity, the random effects model would serve as the choice of method for pooling the effect sizes, as in this latter situation, the fixed effect method is not appropriate for summarising the studies (Egger 1997b, Petitti 1994, Deeks 2001).

Unit of analysis issues
Continuous/interval data
Some studies of SSRIs versus placebo were four arm studies of three fixed dose drug arms and one placebo arm. In such cases for continuous data, mean change (or mean end score) and relevant SDs for three fixed doses were pooled to create one arm for the drug, thus effectively changing the study to a two arm study. This was done to study the effect of mean dose of drug versus placebo. Also, use of one of the drug arms versus placebo would reduce power. However,different dose arms versus placebo could be used in a separate set of meta-analyses to investigate indirect comparison of effect sizes of different dose level. For the purposes of the current review, this has not been done, but will be considered in a future update of the review.

Dichotomous data
Where relevant, the number of events and their denominator were pooled for three fixed doses to create one arm for the study, thus effectively changing the study to a two-arm study (as mentioned above in relation to continuous data).

Assessment of publication bias
Funnel plots were generated by plotting relative risk (RR) against the standard error (SE) of log RR. As three of the included studies did not give response rate data, WMD (available for all 17 included studies) was also plotted against SE of WMD. Essentially a funnel plot allows investigation of whether effect size varies by study size (i.e. tendency of small studies to show larger treatment effects), and indirectly investigates influence of such factors as publication bias, heterogeneity of studies or variation in methodological quality of studies (Egger 1997a).

Assessment of heterogeneity and subgroup differences
For each meta-analysis, the sum of Chi-square values for within sub-categories (strata) heterogeneity was subtracted from the Chi-square value for the whole sample heterogeneity, to find out the residual Chi-square for between sub-category heterogeneity. Thus the significance of the difference between subcategories (strata) was decided from the size of the residual Chi-square and degrees of freedom. For example for one degree of freedom, a Chi-square value of 3.84 and above would prove that there was a statistically significant difference between the sub-categories compared. Criteria for interpreting the heterogeneity test were as follows: no heterogeneity $p > 0.1$, borderline heterogeneity $p = \text{or} < 0.1$ but > 0.05 and definite heterogeneity $p = \text{or} < 0.05$. Additionally, the I-squared test was used to assess inconsistency between studies due to heterogeneity (Higgins 2006). If there was evidence of notable clinical heterogeneity or of statistical heterogeneity, further analysis was to be carried out to identify the sources of such heterogeneity in terms of patient, treatment or study design and quality characteristics (Thompson 1994)

Subgroup analyses and exploration of heterogeneity
Assessment of studies in terms of clinical heterogeneity was carried out qualitatively (using knowledge of the subject area and study design) with a view to deciding whether the studies were too heterogeneous to carry out statistical synthesis (meta-analysis). It was planned a priori to explore reasons for clinical heterogeneity. It was also decided a priori to explore relationship of effect sizes to clinically meaningful subgroups, even if clinical heterogeneity was not present.
Subgroups considered a priori for subgroup analysis were as follows:.
1) different drugs within SSRIs group (citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline)
2) age of participants
3) severity of OCD
4) duration of OCD
5) presence of severe secondary depression
6) different dosage levels
7) duration of trial

Sensitivity analyses
A priori sensitivity analyses were planned in relation to some of the study design characteristics. The following study quality components were identified for exploration in sensitivity analyses:
1) concealment of allocation
2) blinding
3) extent of dropouts.

RESULTS

Description of studies

Results of search
A total of 41 studies were identified. Of these, 17 have been included (Chouinard 1990; Dominguez 1991; Goodman 1989; Goodman 1996; Greist 1992b; Hollander 2002; Hollander 2003; Jenike 1990a; Jenike 1990b; Jenike 1997; Kamijima 2004; Kasper 1999; Kronig 1999; Montgomery 1993c; Nakajima 1996; Ushijima 1997; Zohar 1996), 13 excluded (Ansseau 1996; Beasley 1992; Cottraux 1990; George 1991; Greist 1990; Hohagen 1998; Koran 1996; Koran 1999; Mallya 1993; Peter 1997; Romano 1998; Turner 1985; Zohar 1994) and 11 studies are still awaiting assessment (Bolt 1992; Erzegovesi 2001; Greist 1992a; Hembree 2003 a; Jianxun 1998; Mallya 1992;

Nakagawa 2004; O'Connor 2006 a; Perse 1987; Stein 2007; Wheadon 1993).

Settings

Fifteen out of 17 studies were multi-centre in location. The remaining two did not give information about whether they were single or multicentre. Six studies selected their patients from outpatient settings, three from inpatients and outpatients, and the rest did not give any information about the source of their samples.

Participants

All studies used similar diagnostic criteria for OCD i.e. DSM III or a later version of this system. All studies included either less than severe or severe secondary depression as a co-morbid disorder (severity of depression of was measured on the basis of guidelines relating to respective depression measurement instruments used in the trials). Age of participants in general was 17 years or above (some studies did not provide information on age range). Thus the studies varied in terms of how they chose to give information on age (e.g. minimum, range or mean etc). All studies included both men and women.

Interventions

Five studies compared sertraline against placebo (Chouinard 1990, Greist 1992b, Jenike 1990b, Kronig 1999, Ushijima 1997). Five studies examined fluvoxamine against placebo (Goodman 1989, Goodman 1996, Nakajima 1996, Hollander 2002, Jenike 1990a). A further three studies compared fluoxetine against placebo (Dominguez 1991, Jenike 1997, Montgomery 1993c), with three studies comparing paroxetine against placebo (Hollander 2003, Zohar 1996, Kamijima 2004) and one study examining citalopram (Kasper 1999).

The duration of trials varied from six to 13 weeks.

Outcomes

All studies used YBOCS as the primary efficacy measure, which was used mainly as a continuous scale. Some studies provided dichotomous response rate data, using a cut-off point of percentage reduction on YBOBS, which commonly was 25%, although one study used a cut-off of 35%. Some studies provided a dichotomous response rate using a global scale such as CGI, or both a global scale and YBOCS. Four studies did not report response rate data. Studies varied widely in terms of choice of other OCD scales. However, all studies included a measure of global improvement. Only one study used a scale related to functioning/quality of life.

Data available for meta-analysis

Primary outcomes

Primary continuous outcome (change in YBOCS)

The data required for meta-analysis of continuous variables were mean change in the baseline score in each comparison group and standard deviation (SD) of the mean change and sample size of each group. Seven studies provided these data (Chouinard 1990, Goodman 1996, Greist 1992b, Hollander 2002, Kasper 1999, Montgomery 1993c, Zohar 1996). Kamijima 2004. Dominguez 1991 and Hollander 2003 provided mean change in the form of bar charts with standard errors as whisker extensions. A ruler was used to work out the values for mean change and the standard error of mean for each group. The SD for the mean change score was calculated from the standard error of the mean. Jenike 1997, Goodman 1989, Jenike 1990a, Jenike 1990b, Nakajima 1996 and Ushijima 1997only gave baseline scores with SD and end of treatment scores with SD. For these studies, end of treatment mean score and its SD was used for pooling the results. Kronig 1999 provided mean change in the form of a figure with no SD or standard error. The standard deviation for this study was calculated using F value for the difference between sertraline and placebo group. Thus it was possible to extract usable data for this outcome for all 17 included studies.

Primary dichotomous outcome (response rate)

Dichotomous response rate data were available in all but four studies (Jenike 1997, Jenike 1990a, Jenike 1990b and Hollander 2003). Response was defined as 25% reduction in YBOCS in studies by Kasper 1999 and Ushijima 1997. Dominguez 1991 defined response as 35% reduction in YBOCS. Montgomery 1993c defined response rate as 25% reduction in YBOCS and a CGI score of 1 or 2 (i.e. very much improved or much improved respectively). Eight studies defined response as much improved or very much improved on CGI improvement scale (Goodman 1989, Goodman 1996, Chouinard 1990, Greist 1992b, Kamijima 2004, Ushijima 1997, Nakajima 1996, Kronig 1999). One study gave response rate data using all three criteria i.e. YBOCS reduction of 25%, 35% and CGI score of 1 or 2. The last criterion was used in the meta-analysis as it is the most common criterion used by other studies.

Thus the primary dichotomous variable was differently defined by different studies. The Clinical Global Impression (CGI) scale based definition of response rate (using cut off points of very much or much improved) would be more stringent than 25% reduction in YBOCS. However, studies did not provide information or data on how these two criteria of response rate would compare. Similarly, a 35% reduction in YBOCS is more stringent than the 25% reduction in this scale. Again, there was no information available from the studies as to how this definition compared with the CGI based definition (thus one of the reasons for choosing the random effective model for pooling the data was to take this heterogeneity into account).

Secondary continuous outcomes

Secondary continuous outcome measures used by studies included in the review included Clinical Global Impression (CGI) Scales (both severity and improvement scales), National Institute of Mental Health Obsessive Compulsive Scale (NIMH-OCS), Comprehensive Psychopathological Rating Scale Obsessive Compulsive Subscale (CPRS-OCS), Patient Global Improvement Scale (PGIS) Maudsley Obsessive Compulsive Inventory (MOCI) and Symptom Checklist 90 (SCL90) (APA 2000; Goodman 1998). The former three are observer rated and the latter three are self rated. CGI, NIMH-OCS and PGI are one question non-symptom related severity of illness related scales and the other three are symptom related scales (and not so much severity related scales). CPRS-OCS, PGIS and MOCI were used by only two out of the 17 selected studies and SCL-90 was used by only one study. The CGI severity scale was used and appropriate data provided by Kasper 1999, Montgomery 1993c, Dominguez 1991, Greist 1992b and Chouinard 1990. The CGI improvement scale was used and appropriate data provided by Hollander 2002. However, other studies that used the CGI scale either did not provide usable data, or in the case of Jenike 1997, Jenike 1990a and Jenike 1990b, it was not clear whether they had used CGI Improvement Scale, the CGI Severity Scale or some other global assessment scale.

The most commonly available secondary continuous outcome measure was National Institute of Mental Health Obsessive Compulsive Scale (NIMH-OCS). This was used in the studies by

Chouinard 1990, Goodman 1996, Greist 1992b, Jenike 1990a, Jenike 1990b, Jenike 1997, Kasper 1999, Kronig 1999 and Zohar 1996. With the exception of Kronig 1999 (which did not provide any relevant SD or other data to calculate the SD) all other studies provided usable data. For the two studies that did not use this scale (Montgomery 1993c, Dominguez 1991), usable data was available for the other global assessment scale i.e. CGI severity scale. Therefore, it was decided to use the data for NIMH-OCS as the global outcome scale for the eight studies identified above and the data from CGI severity scale for the remaining two studies

For NIMH-OCS, mean change and SD was available for Kasper 1999, Goodman 1996, Zohar 1996, Chouinard 1990 and Greist 1992b. For Jenike 1997, Jenike 1990a and Jenike 1990b, the end of treatment score and its SD was used for meta-analysis. Montgomery 1993c provided the mean change with SD for CGI severity scale. Dominguez 1991 provided the CGI scale data as the mean change and the standard error of mean in a bar chart with whisker extensions, from which mean change and SD was calculated. In the studies by Kronig 1999 and Goodman 1989, CGI severity scale data were not available (and in the case of the former NIMH-OCS data also were not available), therefore, these studies were not included in the meta-analysis of this outcome. For Hollander 2002, NIMH-OCS and CGI severity data were not available.

Studies awaiting assessment

1. Bolt 1992 Conference proceeding, two RCTs of Fluvoxamine versus placebo, usable data was not available from the abstract.
2. Greist 1992a Conference proceeding, RCT of Fluvoxamine versus placebo, usable data was not available from the abstract.
3. Jianxun 1998 Chinese language trial of Paroxetine versus Clomipramine versus placebo, translation/data extraction of the article is in process
4. Mallya 1992 RCT of fluvoxamine versus placebo, had unusable data (and also perhaps is partial duplicate publication of Goodman 1996 RCT of fluvoxamine versus placebo).
5. Perse 1987 Cross-over study of Fluvoxamine versus placebo, no relevant data was available from the article on pre-crossover period.
6. Wheadon 1993 Conference proceeding, RCT of Paroxetine versus placebo, usable data was not available from the abstract

Letters were sent to Mallya 1992 and Perse 1987 to request the relevant information, and contact is being made with Bolt 1992, Greist 1992a, Wheadon 1993 to obtain the relevant information.

An additional five studies were identified from the search, which are potentially relevant to the review (Erzegovesi 2001, Hembree 2003 a, Nakagawa 2004, O'Connor 2006 a, Stein 2007). These studies, together with the six studies mentioned above, are listed in 'References to studies awaiting assessment".

Excluded studies

Studies that did not meet all the inclusion criteria (n=13) were categorised as excluded studies, and are presented in the Characteristics of excluded studies table.

Risk of bias in included studies

Study design

All studies were parallel group randomised controlled trials.

Allocation concealment

Hollander 2003 used computer-generated randomisation by SmithKline and Beecham. None of the other studies gave any description of how randomisation sequence was generated. None of the studies described what precautions were taken to conceal allocation of the patients to study groups. All studies were classified as 'B' according to Cochrane Handbook criteria.

Blinding

All 17 studies described themselves as double blind, however, only one study (Goodman 1989) provided a description of what that meant (and that study in fact was triple blind).

Drop-out

All but one study (Jenike 1997) analysed the data using intention to treat analysis. Some studies did not give clear reasons for all early withdrawals e.g. 'other reasons' or 'protocol violations' were not explicitly described in each case. Seven studies had an overall dropout of 20% or lower (Chouinard 1990,Goodman 1989,Hollander 2003, Jenike 1997, Jenike 1990a, Jenike 1990b, Kasper 1999). All other studies had a dropout rate of more than 20%.

Effects of interventions

Some clinical heterogeneity was judged to be present between the studies in terms of duration of trial, duration of illness and presence of severe secondary depression, and how the outcomes were assessed for dichotomous response rate data and continuous secondary outcome data. However, the extent of the heterogeneity was not considered to be so severe such that carrying out meta-analysis would be inappropriate. As stated in the methods, because of the clinical heterogeneity, the random effects model was used as the method of choice for pooling results. Where only one study was involved in a meta-analysis (in sub-group analyses or in some cases, adverse effects outcomes), the fixed effects method was used.

SSRIs VERSUS PLACEBO: PRIMARY OUTCOME

This comparison presents the meta-analysis of primary outcomes (reduction in symptoms and treatment responders) for included studies across all five SSRI drugs, together with a meta-analysis for each SSRI drug individually, and sub-group and sensitivity analyses across combined SSRI drugs.

Reduction in YBOCS scores (Comparison 01 01 and Comparison 01 02)

The results, using weighted mean difference (WMD) and random effects (RE) model, were as follows: overall pooled effect size of all SSRIs against placebo (17 studies, 3097 participants) was -3.21 (95% CI -3.84 to -2.57) in favour of SSRIs. For individual SSRI drugs, WMD for citalopram was -3.63 (95% CI -5.20 to -2.06, n=401), WMD for fluoxetine was -3.07 (95% CI -5.32 to -0.82, n=606), WMD for fluvoxamine was -3.87 (95% CI -5.69 to -2.04, n=566), WMD for paroxetine was -3.36 (95% CI -4.55 to -2.17, n=833) and WMD for sertraline was -2.45 (95% CI -3.54 to -1.35, n=691). Thus, all SSRIs as a group of drugs were shown to be effective for OCD symptoms versus placebo, and all the drugs individually showed significant effect sizes of reasonable magnitude, with narrow confidence intervals for citalopram, fluvoxamine, paroxetine and sertraline, and with slightly wider confidence intervals for fluoxetine studies. All five drugs showed a similar degree of benefit, with the difference between WMD of the five individual SSRI drugs shown not to be significantly different, as indicated by the residual Chi-square.

Heterogeneity tests using random effects model were carried out. The heterogeneity test for all SSRIs as a whole group was not significant (Chi-square 21.61, df 16, p = 0.16; I^2 26.0%). The citalopram sub-category included only one study, therefore heterogeneity assessment was not relevant. The heterogeneity test was not significant for paroxetine studies (Chi-square 2.31, df 2, p=0.31, I^2 13.6%). For fluvoxamine studies, the Chi-square test was not significant, but the I^2 was 56%, showing inconsistency due to heterogeneity (Chi-square 9.10, df 4, p=0.06; I^2 56%). Significant heterogeneity was indicated for fluoxetine studies (Chi-square 6.17, df 2, p =0.05; I^2 67.6%). The heterogeneity test was not significant for sertraline studies (Chi-square 1.7, df 4, p=0.79; I^2 0%).

Treatment responders (Comparison 01 03 and 01 04)
Results were as follows: the overall relative risk (RR) across all five SSRI studies (13 studies, 2697 participants) was 1.84 (95% CI 1.56 to 2.17). The RR for response rate in the citalopram group was 1.58 (95% CI 1.20 to 2.08), for fluoxetine was 2.41(95% CI 1.18 to 4.91), for fluvoxamine was 2.68 (95% CI 1.58 to 4.56), for paroxetine was 1.74 (95% CI 1.28 to 2.36), and for sertraline was 1.54 (95% CI 1.20 to 1.99). Thus three SSRIs (citalopram, paroxetine, sertraline) showed similar effect sizes of between 1.54 to 1.74, and fluvoxamine and fluoxetine showed larger effect sizes. However, lower limits of the confidence intervals of effect sizes of all five drugs individually were comparable, and the residual chi-square suggested that the difference between the individual drugs was not significant.

There was no statistical heterogeneity across all SSRIs as a whole group (Chi-square 17.28, df 12, p=0.14; I^2 30.5%) or within four of the five SSRIs analysed as subgroups. There was borderline heterogeneity within the fluoxetine subgroup with a high I^2 (Chi-square 2.76, df 1, p=0.097; I^2 63.7%).

Number needed to treat (NNTs) for SSRIs as a class of drug were calculated (Ebrahim2001). The base rate for calculating NTTs was chosen as 10% (very conservative) and 20% (conservative). The respective NNTs for these rates were 12 and 6.

Subgroup analyses
Subgroup analyses, using the primary outcome of reduction of symptoms, were carried out for duration of OCD, presence of secondary severe depression and duration of trial. All these categories were identified a priori. Other categories intended a priori for subgroup analysis were age, severity of OCD and dose of SSRIs. Age and severity of OCD were similar across studies, therefore no subgroup analyses were possible. Subgroup analyses for low to medium and high doses of SSRIs and dose-response relationship of SSRIs will be investigated in the next update of the review.

Duration of OCD (Comparison 01 05)
Trials with mean duration of OCD of 10 years or less or greater than 10 years were separately meta-analysed. Studies with mean duration of OCD of 10 years or less showed WMD (RE model) of -2.59 (95% CI -3.69 to -1.48). Studies with mean duration of OCD of more than 10 years showed WMD (RE model) of -3.48 (95% CI -4.25 to -2.71). Thus studies using patients with OCD of more than 10 years showed a larger effect size, but this was not significantly different from the effect size of the other sub-group. The test of heterogeneity was non-significant in both subgroups.

Presence of severe secondary depression (Comparison 01 06)
The studies were divided into two sub-groups on the basis of whether or not some patients suffered with severe secondary depression (studies were considered as having a proportion of patients with severe secondary depression, where secondary depression was allowed in the inclusion criteria, and no cut off point on depression scales was used for excluding severe depression or the cut-off point fell within the range of severe depression on the scale used). The WMD (RE model) of studies including some patients with severe secondary depression was -3.60 (95% CI -4.89 to -2.30) and the WMD for studies with no severely depressed participants was -2.84 (95% CI -3.59 to -2.09). However, this difference was not significantly significant. Statistically significant heterogeneity was present in the subgroup of studies that included some patients with severe secondary depression (Chi-square 15.06, df 6, p=0.02; I^2 60.2%).

Duration of trial (Comparison 01 07)
The studies were divided into those with duration of trial of less than 12 weeks and those of 12 weeks or more and were meta-analysed separately. For the studies with duration of trial of less than 12 weeks (duration range for these was 6 to 10 weeks) WMD (RE model) was -2.92 (95% CI -4.13 to -1.72); and for those with duration of trial of 12 weeks or more (duration range for these was 12 to 13 weeks) the WMD was -3.38 (95% CI -4.05 to -2.71). Thus the trials of longer duration showed a larger effect size, but the difference between the two sub-groups was not statistically significant. Heterogeneity was non-significant in both sub-groups.

Sensitivity analyses
Sensitivity analysis using the primary outcomes of reduction in symptoms and response rate were carried out for the only available quality component of proportion of discontinuers

Proportion of discontinuers (Comparison 01 08 and 01 09)
Studies with 20% or less discontinuers were compared with those with more than 20% discontinuers in term of effect size. The former showed a WMD of -3.27 (95% CI -4.45 to -2.10) and the latter of -3.18 (95% CI -3.98 to -2.38). Although this difference was not statistically significant (perhaps due to intention to treat analysis), the higher mean effect in the former would be expected, as patients staying in trials would be more likely to continue to improve than those who drop out early, thus their last observation carried forward would tend to minimize effect size. Heterogeneity was non-significant in both subgroups.

This analysis was also carried out using response rate per completers (i.e. using non-intention to treat analysis data) to see whether the magnitude of discontinuers showed any effect on the effect sizes. Effect size (RR) using random effects model were essentially similar between the two subgroups. In studies with 20% or less discontinuers, it was 1.96 (95% CI 0.96 to 4.00) and in more than 20% discontinuers it was 1.90 (95% CI 1.45 to 2.48); however the former group showed statistically non-significant effect size. Heterogeneity was significant in the subgroup of studies with more than 20% discontinuers (Chi-square 25.53, df 8, p= 0.001; I^2 68.7%).

SSRIs VERSUS PLACEBO: SECONDARY OUTCOMES
The most common secondary outcome measure used by studies, and for which usable data was also available, was the National Institute of Mental Health Obsessive Compulsive Scale (NIMH-OCS), which was employed by eight studies. Two studies, Montgomery 1993c, Dominguez 1991, did not use NIMH-OCS.

However, Montgomery 1993c used Clinical Global Impression Severity Scale (CGI-S scale), and Dominguez 1991 used Clinical Global Impression Improvement Scale (CGI-I scale), and all provided usable data. The remaining two studies did not provide usable data on either of the scales or some other similar scale i.e. observer rated severity related scale.

Meta-analysis was conducted with the eight studies that used the NIMH-OCS and also including the additional two studies that used either NIMH-OCS or CGI scales separately.

Using NIMH-OCS (Comparison 02 01)
The overall WMD (RE model) for all SSRI drugs combined was -0.89 (95% CI -1.13 to -0.64). The WMD for the five SSRI drugs individually was as follows: citalopram -1.13 (95% CI -1.67 to -0.59), fluoxetine -0.20 (95% CI -0.98 to 0.58), fluvoxamine -0.99 (95% CI -1.54 to -0.44), paroxetine -1.10 (95% CI -1.80 to -0.40) and sertraline -0.81 (95% CI -1.22 to -0.40).Thus the effect size for fluoxetine did not differ significantly from placebo (however a sensitivity analysis using the fixed effects model was significant at -0.45 (95% CI -0.63 to -0.27).

Test of heterogeneity for the combined SSRIs group was not significant (Chi-square 4.69, df 7, p= 0.70; I^2 0%) and was also not significant for individual SSRIs.

Using NIMH-OCS or CGI scales (Comparison 02 02)
Using the standardised mean difference (SMD), the overall SMD (RE model) for the combined SSRI drugs group was -0.42 (95% CI -0.52 to -0.33). Using SMD for the individual SSRI drugs, the findings were as follows: citalopram -0.44 (95% CI -0.67 to -0.21), fluoxetine -0.36 (95% CI -0.80 to 0.08), fluvoxamine -0.42 (95% CI -0.61 to -0.23), paroxetine -0.38 (95% CI -0.62 to -0.14) and sertraline -0.41 (95% CI -0.62 to -0.20). Thus the effect size for fluoxetine only was statistically not significant from placebo (however using fixed effects model this was significant at 0.45 (95% CI -0.63 to -0.27).

Test of heterogeneity for the combined SSRIs group was not significant (Chi-square 10.03, df 10, p=0.44; I^2 0.3%). For individual studies, heterogeneity was significant for fluoxetine (Chi-square 8.89, df 2, p= 0.01; I^2 77.7%).

Other secondary outcomes
Only one study provided data on quality of life or social and occupational functioning (Kasper 1999). No studies were long-term trials, therefore the proportion of relapses was not investigated.

SSRIs VERSUS PLACEBO: ADVERSE EFFECTS
Adverse effects were analysed separately for each drug, as this was considered to be clinically more meaningful than combining them across all drugs. These were analysed as overall adverse effects, the three most common adverse effects as reported for each drug by each study, and specific sexual side effects. Not all studies reported adverse effects for each of these three categories. Sexual side effects as a category were analysed separately regardless of whether or not they were reported as the most common side effects, because of their potential impact on patients' lives. Relative risk of adverse effects was calculated using the random effects model.

Adverse Effects Of Citalopram Versus Placebo (Comparison 03 01 to 03 03)
Overall adverse effects
Relative risk for overall adverse effects with citalopram compared to placebo was 1.22 (95% CI 1.02 to 1.45), thus the risk for adverse effects with citalopram as an overall rate was not much higher than placebo. Absolute rate for overall adverse effects for citalopram was 71% and for placebo was 58%.

Common adverse effects
The most common adverse effects reported for citalopram were nausea, headache and insomnia.
Relative risk of nausea for citalopram compared to placebo was 2.47 (95% CI 1.28 to 4.77). Thus, the average risk for experiencing nausea was quite high with citalopram as compared to placebo, but wider confidence intervals suggest that some patients would have much lower and others much higher likelihood of getting this side effect. The absolute rate of nausea for citalopram was 22% and for placebo was 9%. The RR of headache for citalopram versus placebo was 1.05 (95% CI 0.63 to 1.76), with an absolute rate of 17% for citalopram and of 16% for placebo. The RR of insomnia for citalopram compared to placebo was 2.26 (95% CI 1.06 to 4.84), with an absolute rate of 16% for citalopram and 7% for placebo.

Sexual side effects
Relative risk of reported sexual side effects for citalopram versus placebo was high, at 18.64, with very wide 95% CI of 1.15 to 302.80. In absolute terms, 9% patients on citalopram experienced side effects compared to 0% in the placebo group.

Adverse Effects Of Fluoxetine Versus Placebo (Comparison 03 04)
Overall adverse effects
These were not reported by fluoxetine studies.

Common adverse effects
The most common adverse effects as reported by different studies were nausea, headache, insomnia and anxiety.
Risk of these side effects for fluoxetine was similar to placebo, with the RR (RE model) for these three side effects shown to be between 1.11 and 1.42, and 95% confidence intervals crossing 1.

Sexual side effects
These were not reported by fluoxetine studies.

Adverse Effects Of Fluvoxamine (Comparison 03 05 to 03 07)
Overall adverse effects
Relative risk of overall adverse effects for fluvoxamine versus placebo was 1.14 (95% CI 1.07 to 1.21). Thus the risk of overall adverse effects with fluvoxamine differed little from placebo, with an absolute rate of 95% in fluvoxamine was 95% and 83% for placebo.

Common adverse effects
The most common adverse effects across studies were insomnia, nausea, fatigue, headache, somnolence and asthenia.
Fatigue and headache rates were not significantly different between fluvoxamine and placebo. For fatigue, the absolute rate for 28% in the fluvoxamine group compared to 15% in placebo group. For headache, the absolute rates were 18% in the fluvoxamine group and 22% in the placebo group. For insomnia, RR of insomnia for fluvoxamine compared to placebo was 1.81 (95% CI 1.26 to 2.60), with an absolute rate of 34% for fluvoxamine and 18% for placebo. The RR for nausea was 2.64 (95% CI 1.75 to 3.98), with an absolute rate of 31% in the fluvoxamine group and 12% for placebo. The RR for somnolence in the fluvoxamine group compared to

placebo was 2.46 (95% CI 1.59 to 3.79), with an absolute rate of 29% for fluvoxamine and 12% for placebo. The RR of asthenia in fluvoxamine compared to placebo was 2.83 (95% CI 1.74 to 4.60), with an absolute rate of 26% for fluvoxamine and 9% for placebo.

Sexual side effects

Relative risk of sexual side effects in fluvoxamine compared to placebo was 4.02 (95% CI 1.85 to 8.73). In absolute terms, the sexual side effects rate in the fluvoxamine group was 14% and in placebo was 3%.

Adverse Effects Of Paroxetine (Comparison 03 08 to 03 10)

Overall adverse effects

Relative risk of overall adverse effects for paroxetine was 1.14 (95% CI 0.91 to 1.42), showing a lack of significant difference compared with placebo, and with an absolute rate of 81% in the paroxetine group and 72% in the placebo group.

Common adverse effects

The most common side effects reported across studies were asthenia, headache, insomnia and somnolence, nausea and constipation.

Relative risk for asthenia and headache for paroxetine versus placebo was not statistically significant. However RR for the other four adverse effects was significantly higher for paroxetine than placebo as follows: for insomnia 1.71 (95% CI 1.15 to 2.53), for somnolence 1.85 (95% CI 1.12 to 3.06), for nausea 3.96 (95% CI 1.82 to 8.61) and for constipation 4.29 (95% CI 1.26 to 14.56). The absolute rate of asthenia for paroxetine was 26% and for placebo was 18%, the absolute rate of headache for paroxetine was 24% and for the placebo group was 26%, the absolute rate of insomnia for paroxetine was 23% and for placebo was 14% and the absolute rate of somnolence for paroxetine was 27% and for placebo was 11%.

Sexual side effects

These were reported in usable form for only one study (Kamijima 2004). The RR of sexual side effects for paroxetine did not significantly differ from placebo (RR 6.93 CI 0.36 to 132.39), with the absolute rate of 3% for paroxetine and of 0% for placebo.

Adverse Effects Of Sertraline (Comparison 03 11 to 03 13)

Overall Adverse Effects

Relative risk for overall adverse effects for sertraline was 1.21 (95% CI 1.08 to 1.37). The absolute rate of overall adverse effects for sertraline was 87% and for placebo was 68%.

Common adverse effects

The most common adverse effects as reported by different sertraline studies were nausea, insomnia, dyspepsia, constipation, sedation, forgetfulness, headache and diarrhoea.

Two adverse effects, insomnia and diarrhoea, showed significant RR for sertraline compared to placebo. The RR of insomnia for sertraline compared to placebo was 2.23 (95% CI 1.09 to 4.56), with an absolute rate for sertraline of 31% and for placebo of 13%. Relative risk of diarrhoea for sertraline compared to placebo was 2.16 (95% CI 1.11 to 4.23), with an absolute rate of 25% for sertraline and of 10% for placebo. The RR for nausea, dyspepsia, constipation, sedation, forgetfulness and headache for sertraline compared to placebo were not significant as their confidence intervals crossed 1.

Sexual side effects

Relative risk for sexual side effects for sertraline compared to placebo was 5.74 (95% CI 0.68 to 48.31). The confidence interval crossed 1, thus showing no significant risk difference between sertraline and placebo. Absolute rates for sexual side effects for sertraline was 14% and for placebo was 2%. However this difference was not statistically significant.

Dose response relationship for side effects

This was not investigated in the current issue of this systematic review, but will be considered in a future update of this review.

Funnel Plots

These were carried out using both dichotomous measures and continuous measures for YBOCS. It is customary to generate funnel plots only using dichotomous measures but as the binary measures for YBOCS were not available for four of the 17 studies, plots were also generated for the continuous measure. The funnel plots did not show gross asymmetry, although both reflected an absence of small (both negative and positive) studies (Figure 1, Figure 2), therefore, the shapes of the funnel plots did not suggest publication bias in the topic reviewed.

Figure 1. Funnel plot 1.

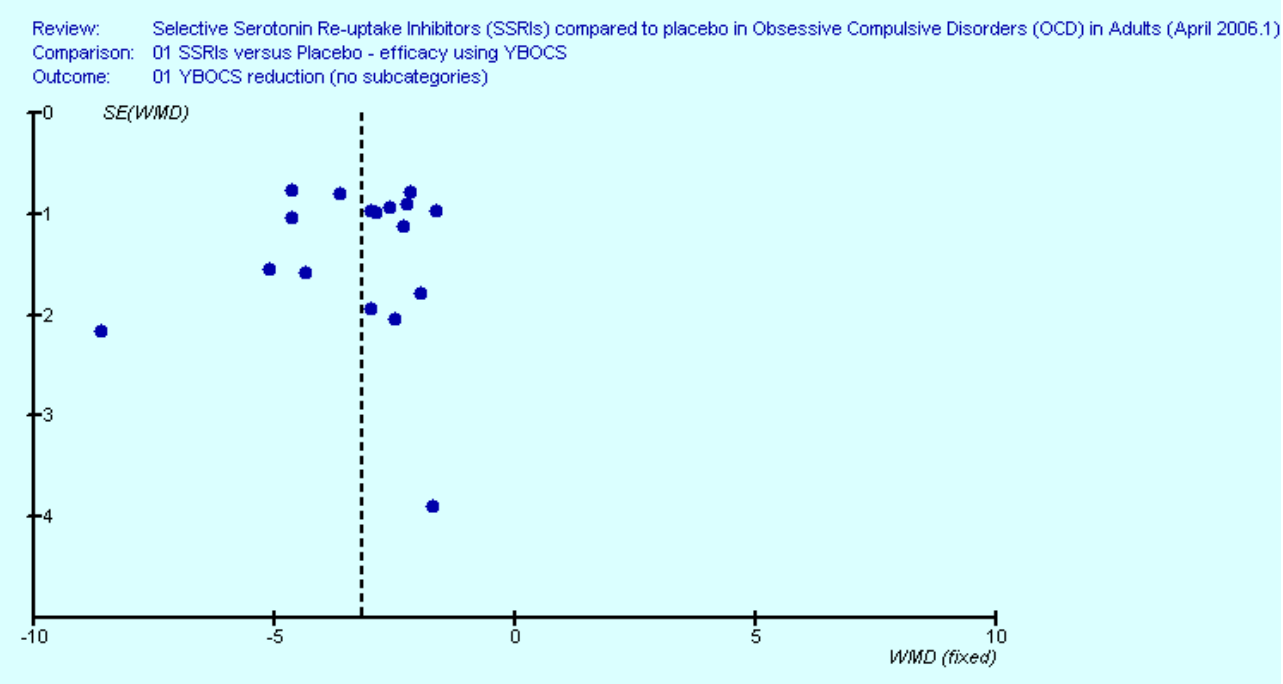
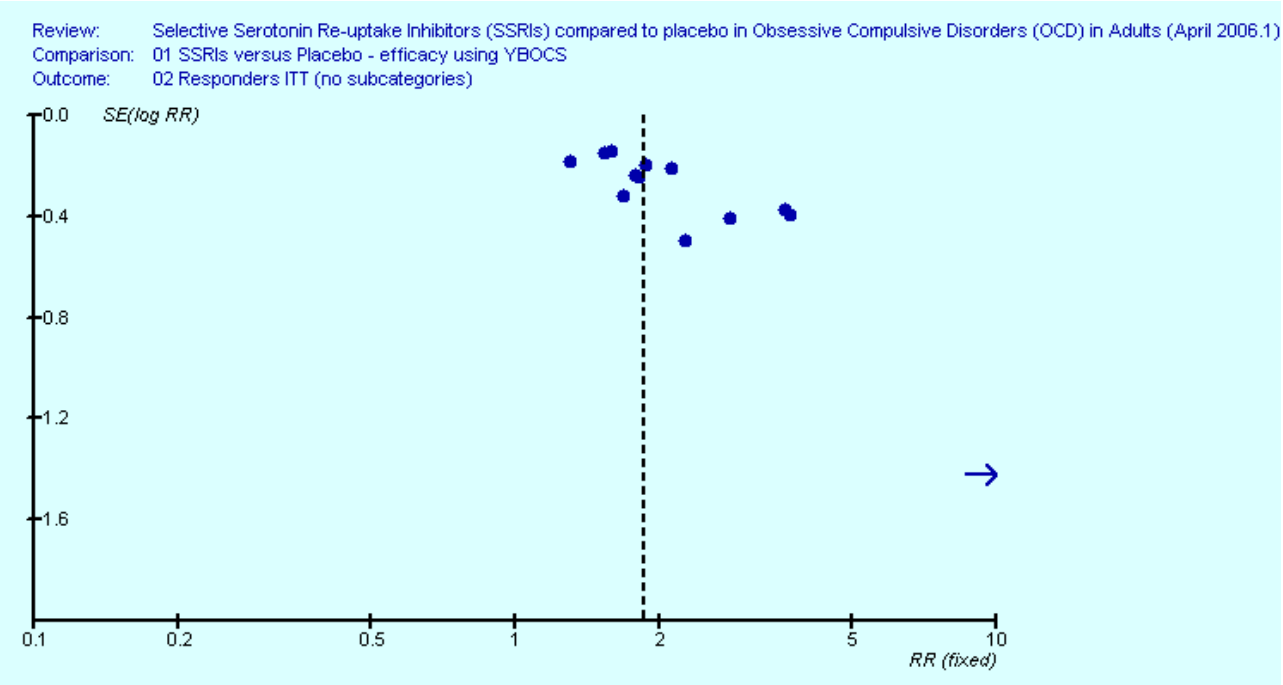


Figure 2. Funnel plot 2.



DISCUSSION

Summary of findings

Seventeen RCTs of SSRIs versus placebo (involving a total of 3097 patients) were included in this systematic review and meta-analysis. Meta-analyses of the available data using a random effects model demonstrated that SSRIs, as a class of drugs, and individually were significantly more effective than placebo for the treatment of OCD, both in terms of continuous (using YBOCS) and dichotomous (response rate using YBOCS and global impression scales) outcomes. The pooled effect sizes of all five individual SSRIs were similar, although it should be noted that these sorts of indirect comparisons of different drugs are unreliable due to the potential effects of confounding (Bucher 1997). Results for studies using

alternative scales to measure continuous outcome (NIHM-OC scale, CGI-S and CGI-I) broadly supported these findings. Studies using these scales indicated that, with the exception of fluoxetine, all SSRI drugs were more effective than placebo in adults with OCD. The lack of conclusive data for fluoxetine may be due to the insensitivity of the outcome measure, to the fact that this was not the primary outcome measure, or it may simply be a chance finding.

The three most common adverse effects for each SSRI reported in each RCT were analysed. These included nausea, dyspepsia, diarrhoea, constipation, headache, insomnia, anxiety, fatigue, sedation, somnolence, asthenia and forgetfulness. Although reported adverse effect data were limited, with few exceptions, the overall and individual adverse effects for the different SSRIs were always worse than for placebo and, in the majority of cases, the difference was statistically significant. The most common adverse effect was nausea. Included studies were fairly clinically and methodologically homogeneous, although some clinical heterogeneity was observed in terms of trial duration, illness duration, methods for assessing dichotomous and continuous outcomes, and the presence of severe secondary depression in some patients.

The effect of SSRIs in achieving improvement of OCD symptoms is modest, and the clinical utility of these interventions should be weighed against the adverse effects, particularly those that impact on quality of life, such as sexual adverse effects.

Subgroup analyses

It should be noted that this small sample of 17 studies lacks sufficient power for firm conclusions to be drawn from any sub-group analysis, and these analyses should be seen as hypothesis-generating only. Analysis by duration of illness (10 year or more), duration of trials (12 weeks of longer) and presence of severe secondary depression suggested that these drugs might be equally effective under these different conditions However, non-statistically significant increased effect sizes were observed in trials involving patients with more chronic illness, presence of severe secondary depression and for longer duration of trials. These observations appear to be plausible. Of particular interest is the observation that patients with OCD and with co-morbid severe secondary depression respond equally well to SSRIs as those without co-morbid severe secondary depression. Presence of severe secondary depression in OCD is a poor predictor of response to behaviour therapy (Soomro 2003). Thus in these patients, drug treatment may be the treatment of choice, at least initially.

Quality of included studies

All studies described themselves as randomised without giving details of how the randomisation sequence was generated and what precautions were taken in relation to concealment of allocation. With the exception of one study (which was described as double blind, but gave a clear description of being triple blind (Goodman 1989), all studies were described as double blind without specifying what this meant. As additional information on risk of bias was limited in these studies, the effects of only one component of study quality, the proportion of people who discontinued, was amenable to sensitivity analysis. Sensitivity analysis of the proportion of patients withdrawing from the trials indicated no differences in the pooled effects size between studies with 20% or less discontinuers and studies with more than 20% discontinuers. This is consistent with previous findings (Juni 2001).

Strengths of this review

To limit the potential effects of bias introduced by including observational studies, only randomised or quasi-randomised controlled trials were eligible to be included in the review. The main source of searches for relevant RCTs for this review, the Cochrane Depression, Anxiety and Neurosis Controlled Trials Register (CCDAN-CTR), is the most comprehensive source of trials in this area. Thus, although more recently updated searches have identified some additional trials (included in the Awaiting Assessment category), it is unlikely that relevant trials have been missed. Beyond searches of CCDAN-CTR, no additional published or unpublished reports were identified, either from pharmaceutical companies (through CCDAN) or through direct contact with researchers in the field. Study selection and data extraction process were carried out in duplicate to enhance reliability, with good agreement and few differences between the review co-authors. Sensitivity analysis has been carried out for proportion of discontinuers. Quality assessment was undertaken using a variety of recommendations taken from the Cochrane Reviewer's Handbook, the CONSORT criteria, and other sources.

It should be noted that although primary and secondary outcomes were generally measured using valid instruments, this was not true of adverse effects outcomes. The limited information on adverse effects of SSRIs in general suggests the possible need for a separate systematic review, using Cochrane methodology, of the adverse effects of these drugs across the full range of disorders in which they have been evaluated. Such a review could present a clearer picture of the short-term and common side effects of these drugs. For rare and long-term adverse effects, other designs may need to be considered - such as cohort, case control and case series. It is also worth noting that these studies do not give information about people from different ethnic and cultural backgrounds. Therefore, the generalisability of results to these populations is uncertain.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review provides evidence that SSRIs are moderately effective, at least in the short-term, in adults with OCD of varying duration. Although only limited information was available to guide the ethnic and cross-cultural applications of these findings, the patients included in these trials were thought to be representative of those in clinical practice, including both men and women of difference ages who had suffered OCD over varying lengths of time. Numbers needed to treat (NNT) were calculated assuming that a realistic baseline response rate in the clinical setting (that is, the response rate that may be expected even without treatment) would be between 10 to 20%. Based on the data reviewed here, in a group of patients where 10% might be expected to recover without treatment, 12 patients would need to be treated with SSRIs to achieve improvements for one additional patient, whereas in a group of patients where 20% might be expected to recover without treatment, six patients would need to be treated to achieve improvements for one additional patient. The necessary duration of treatment and the long-term outcomes associated with these interventions have yet to be determined. Although SSRIs should be considered as potentially effective treatments for this population, treatment decisions need to take account of the potential adverse effects of these drugs. In some patients, alternative treatments such as cognitive behavioural therapy may need to be considered (Soomro 2003).

Implications for research

Most of the existing studies in this area were found to be poorly reported and lacking sufficient and useable data for the purposes of secondary analyses and summary. Future work in this field needs to conform to the standards laid out in the revised CONSORT statement (Moher 2001). Future trialists might also consider the collection of data on additional, potentially important outcome measures. Whilst symptom severity and change scores may be useful, the value of information on other outcomes that are of direct relevance to patients, such as quality of life, should not be underestimated. Furthermore, particular consideration should be given to the use of valid and reliable methods for collecting adverse effect data. Finally, trials of longer duration are required to establish the necessary length of treatment and longer term outcomes, and trials involving a diverse range of ethnic and cultural groups would ensure greater generalisability of findings.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chouinard 1990

Methods	Design: RCT parallel group, Blindness: double Duration of study: 8 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM III Co-morbidity allowed: Secondary depression mild Setting: Not described Age: Mean(SD) 36.5(10.7) to 38(12.8) Other characteristics: Men and women
Interventions	No. of arms: Two Sertraline versus placebo
Outcomes	Primary: Change in YBOCS total score

Chouinard 1990 *(Continued)*

	Proportion of responders (defined as CGI of 1 or 2)
Notes	1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dominguez 1991

Methods	Design: RCT parallel group, Blindness: double Duration of study: 13 week
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression including sever Setting: Out-patients Age: 17-70 yrs Other characteristics: Men and women
Interventions	No. of arms: four (fluoxetine 20mg vs 40mg vs 60mg vs placebo)
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as 35% reduction in YBOCS)
Notes	2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goodman 1989

Methods	Design: RCT parallel group, Blindness: double (but in fact triple) Duration of study: 6 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM III Co-morbidity allowed: Secondary depression including sever Setting: Outpatients Age: Mean (SD) 39(14) to 35(11) Other characteristics: Men and women
Interventions	No. of arms: Two - Fluvoxamine versus placebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as CGI of 1 or 2)

Goodman 1989 *(Continued)*

Notes	3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Goodman 1996

Methods	Design: RCT parallel group, Blindness: double Duration of study: 10 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression including sever Setting: Outpatients Age: 18 or above Other characteristics: Men and women
Interventions	No. of arms: Two- Fluvoxamine versus placebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as CGI of 1 or 2)
Notes	4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Greist 1992b

Methods	Design: RCT parallel group, Blindness: double Duration of study: 12 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression mild Setting: Outpatients Age: Mean(SD) 35.9(13) to 40.1(12) Other characteristics: Men and women
Interventions	No. of arms: Four Sertraline 50, 100 and 200mg versus placebo)
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as CGI of 1 or 2)
Notes	5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hollander 2002

Methods	Design: RCT parallel group, Blindness: double Duration of study: 12 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM V Co-morbidity allowed: HAM-D 16 or less Setting: Not known Age: Mean(SE) 36.7(1.0) to 38.1(1.1) Other characteristics: Men and women
Interventions	No of arms: Two Fluvoxamine versus palcebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as much improved or very much improved)
Notes	6

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hollander 2003

Methods	Design: RCT parallel group, Blindness: double Duration of study: 12 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: HAM-D 16 or less on first 17 or 21 items scale, and 2 or less on item 1 Setting: outpatients Age: Mean(SD) 40.0(15.4) to 42.1(12.7) Other characteristics: Men and women; 16 patients from non-white ethnicity
Interventions	No. of arms: four, paroxetine 20mg vs 40mg vs 60mg vs placebo
Outcomes	Primary: Change in YBOCS total score Dichotomous outcome not given
Notes	7

Hollander 2003 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jenike 1990a

Methods	Design: RCT parallel group, Blindness: double Duration of study: 10 wks
Participants	Single or multicentre: Not desribed Diagnostic criteria: DSM III Co-morbidity allowed: Secondary depression including severe Setting: Outpatients Age: Mean(SD) 37.5(9.3) to 34.6(12.9) Other characteristics: Men and women
Interventions	No. of arms: Two- Fluvoxamine versus placebo
Outcomes	Primary: Change in YBOCS total score
Notes	8

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jenike 1990b

Methods	Design: RCT parallel group, Blindness: double Duration of study: 10 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression mild Setting: Not described Age: Mean(SD) 35(14) to 45(13) Other characteristics: Men and women
Interventions	No. of arms: Two Sertraline versus placebo
Outcomes	Primary: Change in YBOCS total score
Notes	9

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jenike 1997

Methods	Design: RCT parallel group, Blindness: double Duration of study: 10 wks
Participants	Single or multicentre: Not described Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression mild Setting: Not described Age: 18 or above Other characteristics: Men and women
Interventions	No. of arms: Three - Phenelzine versus Fluoxetine versus placebo
Outcomes	Primary: Change in YBOCS total score
Notes	10

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kamijima 2004

Methods	Design: RCT parallel group, Blindness: double Duration of study 12 wks
Participants	Single or multicentre: Multicenter Diagnostic criteria: DSM VI Co-morbidity allowed: Secondary depression Setting: Not described Age: 16 to 71 Other characteristics: Men and women
Interventions	No. of arms: Two Paroxentine versus placebo
Outcomes	Primary: Change in YBOCS total score
Notes	11

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kasper 1999

Methods	Design: RCT parallel group, Blindness: double Duration of study: 12 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IV Co-morbidity allowed: Secondary depression mild Setting: not described Age: 18-65 years Other characteristics: Men and women
Interventions	No. of arms: four (citalopram 20mg vs 40mg vs 60mg vs placebo)
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as 25% reduction in YBOCS)
Notes	12

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kronig 1999

Methods	Design: RCT parallel group, Blindness: double Duration of study: 12 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression mild Setting: Outpatient Age: Mean(SD) 35.5(11.2) to 38.1(12.0) Other characteristics: Men and women
Interventions	No. of arms: Two Sertraline versus placebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as CGI of 1 or 2)
Notes	13

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Montgomery 1993c

Methods	Design: RCT parallel group, Blindness: double Duration of study: 8 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression including sever Setting: Not described Age: 18 to 65 years Other characteristics: Men and women
Interventions	No. of arms: four, fluoxetine 20mg vs 40mg vs 60mg vs placebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as 25% reduction in YBOCS and a CGI of 1 or 2)
Notes	14

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Nakajima 1996

Methods	Design: RCT parallel group, Blindness: double Duration of study: 8 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: they did not assess for depression (thus not clear whether some patients were depressed) Setting: In patients and out patients Age: 18 to 69 years Other characteristics: Men and women
Interventions	No. of arms: Three, fluvoxamine 100-150mg (ie low dose) vs fluvoxamine 200-300mg (medium doese) vs placebo

Nakajima 1996 *(Continued)*

Outcomes	Primary: Change in YBOCS total score Proportion of responders defined as improved or much improved
Notes	15

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ushijima 1997

Methods	Design: RCT parallel group, Blindness: double Duration of study: 8 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: they did not assess for depression (thus not clear whether some patients were depressed) Setting: In patients and out patients Age: 18 to 66 years Other characteristics: Men and women
Interventions	No. of arms: Three, Sertraline low dose (25-100mg) vs sertraline high dose (50-200mg) vs placebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders defined as improved or much improved
Notes	16

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Zohar 1996

Methods	Design: RCT parallel group, Blindness: double Duration of study: 12 wks
Participants	Single or multicentre: Multicentre Diagnostic criteria: DSM IIIR Co-morbidity allowed: Secondary depression including sever Setting: Not described Age: 17 or above Other characteristics: Men and women

Zohar 1996 *(Continued)*

Interventions	No. of arms: Three, Paroxetine versus Phenelzine versus placebo
Outcomes	Primary: Change in YBOCS total score Proportion of responders (defined as 25% reduction in YBOCS)
Notes	17

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ansseau 1996	This study was not selected because the patient group studies is obsessive compulsive personality disorder which is not the condition under study
Beasley 1992	This study was not selected because the study reports only suicide as an outcome of fluoxetine in OCD and not the impact of fluoxetine on OCD symptoms.
Cottraux 1990	Combination trial of Fluvoxamine with exposure versus placebo with exposure - thus not direct one to one comparison of Fluvoxamine versus placebo
George 1991	This study was not selected because of co-morbidity Giles de la Tourette Syndrome within OCD patients which was an exclusion criteria
Greist 1990	This study was not selected because the intervention is clomipramine which is SRI and not SSRI.
Hohagen 1998	Combination trial of Fluvoxamine with behaviour therapy versus placebo with behaviour therapy - thus not direct one to one comparison of Fluvoxamine versus placebo
Koran 1996	This study does not report of impact of fluoxetine on OCD symtom.
Koran 1999	This study is single arm trial in the initial phase and then in the subsequest phase investigates in randomised conrolled manner the withdrawal / discontinuation of sertraline
Mallya 1993	This study reports two case reports and is not a randomised controlled trial
Peter 1997	Combination trial of Fluvoxamine and CBT versus placebo and CBT - thus not direct one to one comparison of Fluvoxamine versus placebo
Romano 1998	This study is single arm trial in the initial phase and then in the subsequest phase investigates in randomised conrolled manner the withdrawal / discontinuation of fluoxetine
Turner 1985	This study is not selected because it is a single arm trial. The placebo is used in the initial run-in phase and then fluoxetine is used and no parallel placebo arm is used in the study
Zohar 1994	This trial is not selected because the condition under study is exhibitionism and not OCD

DATA AND ANALYSES

Comparison 1. SSRIs versus Placebo - efficacy using YBOCS

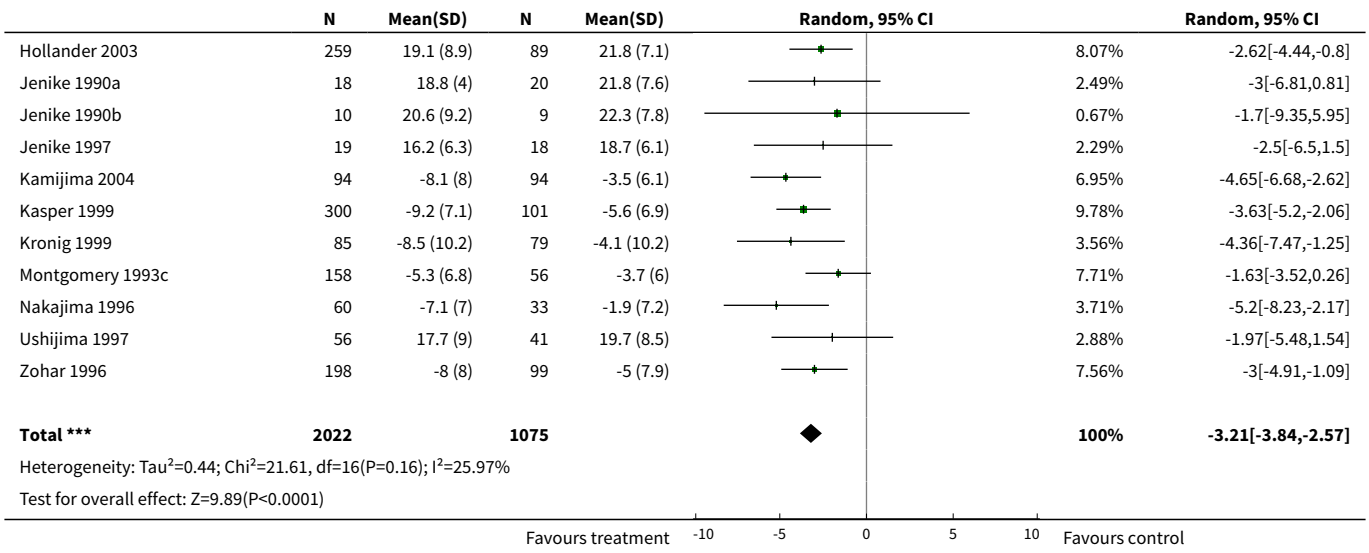
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 YBOCS reduction for all SSRI drugs	17	3097	Mean Difference (IV, Random, 95% CI)	-3.21 [-3.84, -2.57]
2 YOBCS reduction (individual SSRI drugs)	17	3097	Mean Difference (IV, Random, 95% CI)	-3.21 [-3.84, -2.57]
2.1 Citalopram	1	401	Mean Difference (IV, Random, 95% CI)	-3.63 [-5.20, -2.06]
2.2 Fluoxetine	3	606	Mean Difference (IV, Random, 95% CI)	-3.07 [-5.32, -0.82]
2.3 Fluvoxamine	5	566	Mean Difference (IV, Random, 95% CI)	-3.87 [-5.69, -2.04]
2.4 Paroxetine	3	833	Mean Difference (IV, Random, 95% CI)	-3.36 [-4.55, -2.17]
2.5 Sertraline	5	691	Mean Difference (IV, Random, 95% CI)	-2.45 [-3.54, -1.35]
3 Responders ITT for all SSRI drugs	13	2697	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.56, 2.17]
4 Responders ITT (indvidual SSRI drugs)	13	2697	Risk Ratio (M-H, Random, 95% CI)	1.84 [1.56, 2.17]
4.1 Citalopram	1	401	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.20, 2.08]
4.2 Fluoxetine	2	572	Risk Ratio (M-H, Random, 95% CI)	2.41 [1.18, 4.91]
4.3 Fluvoxamine	4	564	Risk Ratio (M-H, Random, 95% CI)	2.68 [1.58, 4.56]
4.4 Paroxetine	2	487	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.28, 2.36]
4.5 Sertraline	4	673	Risk Ratio (M-H, Random, 95% CI)	1.54 [1.20, 1.99]
5 YBOCS reduction (mean duration of OCD)	12	2105	Mean Difference (IV, Fixed, 95% CI)	-3.19 [-3.82, -2.56]
5.1 Mean duration of OCD 10 yrs or less	4	601	Mean Difference (IV, Fixed, 95% CI)	-2.59 [-3.69, -1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Mean duration of OCD more than 10 yrs	8	1504	Mean Difference (IV, Fixed, 95% CI)	-3.48 [-4.25, -2.71]
6 YBOCS reduction (severe secondary depression)	15	2907	Mean Difference (IV, Random, 95% CI)	-3.16 [-3.83, -2.50]
6.1 Studies with some pts with severe sec. depression	7	1290	Mean Difference (IV, Random, 95% CI)	-3.60 [-4.89, -2.30]
6.2 Studies with no pts with severe sec. depression	8	1617	Mean Difference (IV, Random, 95% CI)	-2.84 [-3.59, -2.09]
7 YBOCS reduction (duration of trial)	17	3097	Mean Difference (IV, Random, 95% CI)	-3.19 [-3.81, -2.57]
7.1 Duration of trials less than 12 wks	9	783	Mean Difference (IV, Random, 95% CI)	-2.92 [-4.13, -1.72]
7.2 Duration of trials 12 to 13 wks	8	2314	Mean Difference (IV, Random, 95% CI)	-3.38 [-4.05, -2.71]
8 YBOCS reduction (proportion of discontinuers)	17	3097	Mean Difference (IV, Random, 95% CI)	-3.21 [-3.84, -2.57]
8.1 Studies with 20% or less discontinuers	7	972	Mean Difference (IV, Random, 95% CI)	-3.27 [-4.45, -2.10]
8.2 Studies with more than 20% discontinuers	10	2125	Mean Difference (IV, Random, 95% CI)	-3.18 [-3.98, -2.38]
9 Responders per completers (proportion of discontinuers)	12	1912	Risk Ratio (M-H, Random, 95% CI)	1.86 [1.49, 2.32]
9.1 Studies with 20% or less discontinuers	3	457	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.96, 4.00]
9.2 Studies with more than 20% discontinuers	9	1455	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.45, 2.48]

Analysis 1.1. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 1 YBOCS reduction for all SSRI drugs.

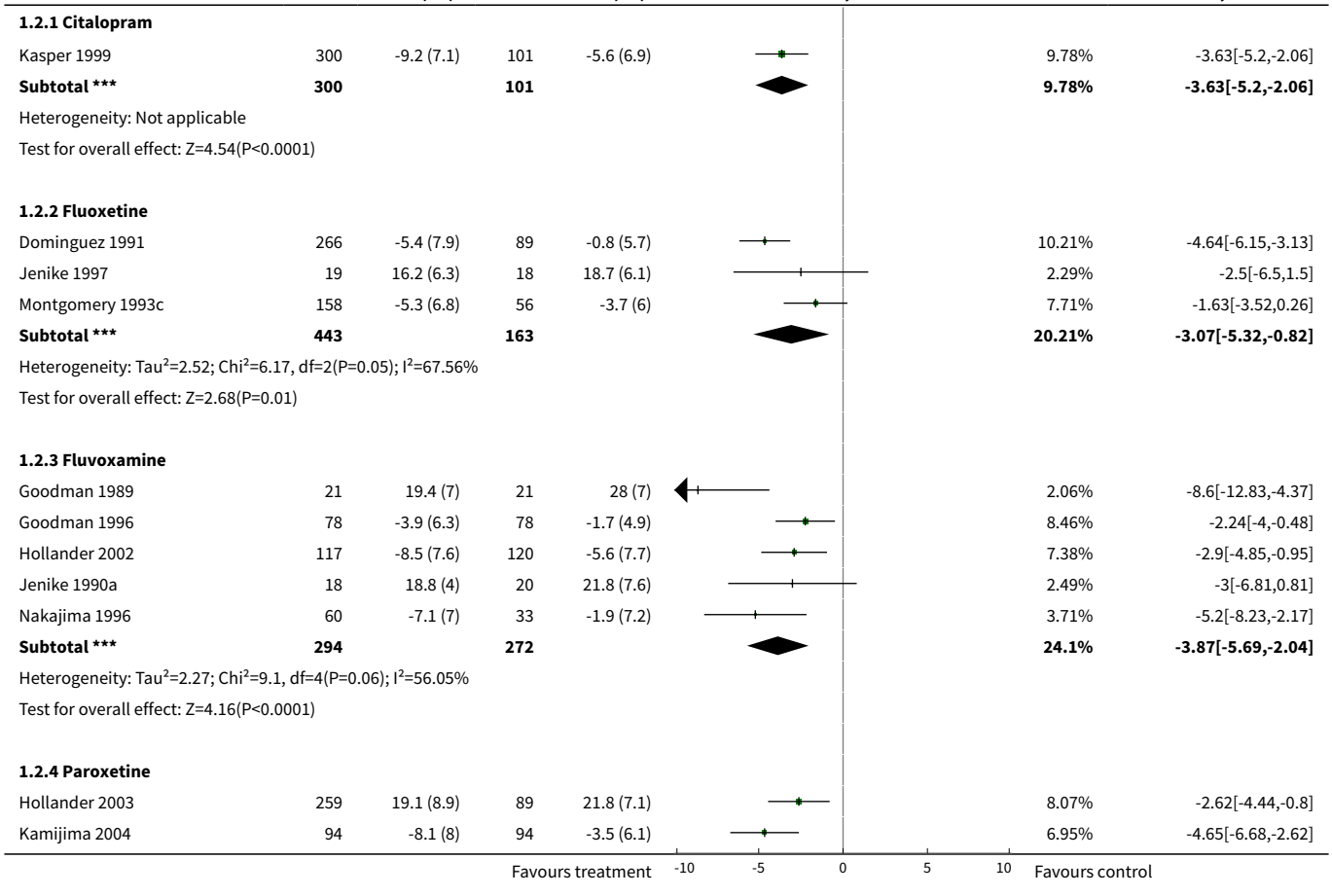
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Chouinard 1990	43	-3.8 (5.2)	44	-1.5 (5.2)		6.22%	-2.31[-4.5,-0.12]
Dominguez 1991	266	-5.4 (7.9)	89	-0.8 (5.7)		10.21%	-4.64[-6.15,-3.13]
Goodman 1989	21	19.4 (7)	21	28 (7)		2.06%	-8.6[-12.83,-4.37]
Goodman 1996	78	-3.9 (6.3)	78	-1.7 (4.9)		8.46%	-2.24[-4,-0.48]
Greist 1992b	240	-5.6 (6.2)	84	-3.4 (6.2)		9.99%	-2.17[-3.71,-0.63]
Hollander 2002	117	-8.5 (7.6)	120	-5.6 (7.7)		7.38%	-2.9[-4.85,-0.95]

Favours treatment — Favours control



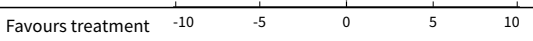
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Hollander 2003	259	19.1 (8.9)	89	21.8 (7.1)		8.07%	-2.62[-4.44,-0.8]
Jenike 1990a	18	18.8 (4)	20	21.8 (7.6)		2.49%	-3[-6.81,0.81]
Jenike 1990b	10	20.6 (9.2)	9	22.3 (7.8)		0.67%	-1.7[-9.35,5.95]
Jenike 1997	19	16.2 (6.3)	18	18.7 (6.1)		2.29%	-2.5[-6.5,1.5]
Kamijima 2004	94	-8.1 (8)	94	-3.5 (6.1)		6.95%	-4.65[-6.68,-2.62]
Kasper 1999	300	-9.2 (7.1)	101	-5.6 (6.9)		9.78%	-3.63[-5.2,-2.06]
Kronig 1999	85	-8.5 (10.2)	79	-4.1 (10.2)		3.56%	-4.36[-7.47,-1.25]
Montgomery 1993c	158	-5.3 (6.8)	56	-3.7 (6)		7.71%	-1.63[-3.52,0.26]
Nakajima 1996	60	-7.1 (7)	33	-1.9 (7.2)		3.71%	-5.2[-8.23,-2.17]
Ushijima 1997	56	17.7 (9)	41	19.7 (8.5)		2.88%	-1.97[-5.48,1.54]
Zohar 1996	198	-8 (8)	99	-5 (7.9)		7.56%	-3[-4.91,-1.09]
Total * **	**2022**		**1075**			**100%**	**-3.21[-3.84,-2.57]**
Heterogeneity: Tau²=0.44; Chi²=21.61, df=16(P=0.16); I²=25.97%							
Test for overall effect: Z=9.89(P<0.0001)							

Analysis 1.2. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 2 YOBCS reduction (individual SSRI drugs).



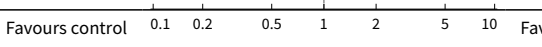
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Citalopram							
Kasper 1999	300	-9.2 (7.1)	101	-5.6 (6.9)		9.78%	-3.63[-5.2,-2.06]
Subtotal * **	**300**		**101**			**9.78%**	**-3.63[-5.2,-2.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.54(P<0.0001)							
1.2.2 Fluoxetine							
Dominguez 1991	266	-5.4 (7.9)	89	-0.8 (5.7)		10.21%	-4.64[-6.15,-3.13]
Jenike 1997	19	16.2 (6.3)	18	18.7 (6.1)		2.29%	-2.5[-6.5,1.5]
Montgomery 1993c	158	-5.3 (6.8)	56	-3.7 (6)		7.71%	-1.63[-3.52,0.26]
Subtotal * **	**443**		**163**			**20.21%**	**-3.07[-5.32,-0.82]**
Heterogeneity: Tau²=2.52; Chi²=6.17, df=2(P=0.05); I²=67.56%							
Test for overall effect: Z=2.68(P=0.01)							
1.2.3 Fluvoxamine							
Goodman 1989	21	19.4 (7)	21	28 (7)		2.06%	-8.6[-12.83,-4.37]
Goodman 1996	78	-3.9 (6.3)	78	-1.7 (4.9)		8.46%	-2.24[-4,-0.48]
Hollander 2002	117	-8.5 (7.6)	120	-5.6 (7.7)		7.38%	-2.9[-4.85,-0.95]
Jenike 1990a	18	18.8 (4)	20	21.8 (7.6)		2.49%	-3[-6.81,0.81]
Nakajima 1996	60	-7.1 (7)	33	-1.9 (7.2)		3.71%	-5.2[-8.23,-2.17]
Subtotal * **	**294**		**272**			**24.1%**	**-3.87[-5.69,-2.04]**
Heterogeneity: Tau²=2.27; Chi²=9.1, df=4(P=0.06); I²=56.05%							
Test for overall effect: Z=4.16(P<0.0001)							
1.2.4 Paroxetine							
Hollander 2003	259	19.1 (8.9)	89	21.8 (7.1)		8.07%	-2.62[-4.44,-0.8]
Kamijima 2004	94	-8.1 (8)	94	-3.5 (6.1)		6.95%	-4.65[-6.68,-2.62]

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Zohar 1996	198	-8 (8)	99	-5 (7.9)		7.56%	-3[-4.91,-1.09]
Subtotal ***	**551**		**282**			**22.58%**	**-3.36[-4.55,-2.17]**
Heterogeneity: Tau^2=0.15; Chi^2=2.31, df=2(P=0.31); I^2=13.56%							
Test for overall effect: Z=5.52(P<0.0001)							
1.2.5 Sertraline							
Chouinard 1990	43	-3.8 (5.2)	44	-1.5 (5.2)		6.22%	-2.31[-4.5,-0.12]
Greist 1992b	240	-5.6 (6.2)	84	-3.4 (6.2)		9.99%	-2.17[-3.71,-0.63]
Jenike 1990b	10	20.6 (9.2)	9	22.3 (7.8)		0.67%	-1.7[-9.35,5.95]
Kronig 1999	85	-8.5 (10.2)	79	-4.1 (10.2)		3.56%	-4.36[-7.47,-1.25]
Ushijima 1997	56	17.7 (9)	41	19.7 (8.5)		2.88%	-1.97[-5.48,1.54]
Subtotal ***	**434**		**257**			**23.33%**	**-2.45[-3.54,-1.35]**
Heterogeneity: Tau^2=0; Chi^2=1.7, df=4(P=0.79); I^2=0%							
Test for overall effect: Z=4.38(P<0.0001)							
Total ***	**2022**		**1075**			**100%**	**-3.21[-3.84,-2.57]**
Heterogeneity: Tau^2=0.44; Chi^2=21.61, df=16(P=0.16); I^2=25.97%							
Test for overall effect: Z=9.89(P<0.0001)							
Test for subgroup differences: Chi^2=2.33, df=1 (P=0.68), I^2=0%							



Analysis 1.3. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 3 Responders ITT for all SSRI drugs.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chouinard 1990	11/43	5/44		2.59%	2.25[0.85,5.94]
Dominguez 1991	76/266	7/89		4.21%	3.63[1.74,7.58]
Goodman 1989	9/21	0/21		0.34%	19[1.18,306.79]
Goodman 1996	26/80	7/80		3.85%	3.71[1.71,8.06]
Greist 1992b	93/241	25/84		11.69%	1.3[0.9,1.87]
Hollander 2002	51/117	28/120		11%	1.87[1.27,2.74]
Kamijima 2004	47/94	22/93		9.93%	2.11[1.39,3.21]
Kasper 1999	174/300	37/101		15.66%	1.58[1.2,2.08]
Kronig 1999	35/85	18/79		8.25%	1.81[1.12,2.92]
Montgomery 1993c	75/160	15/57		8.6%	1.78[1.12,2.83]
Nakajima 1996	31/81	6/44		3.7%	2.81[1.27,6.2]
Ushijima 1997	23/56	10/41		5.54%	1.68[0.9,3.14]
Zohar 1996	109/201	35/99		14.64%	1.53[1.14,2.06]
Total (95% CI)	**1745**	**952**		**100%**	**1.84[1.56,2.17]**
Total events: 760 (Treatment), 215 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=17.28, df=12(P=0.14); I^2=30.54%					
Test for overall effect: Z=7.29(P<0.0001)					



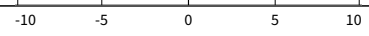
Analysis 1.4. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 4 Responders ITT (indvidual SSRI drugs).

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Citalopram					
Kasper 1999	174/300	37/101		15.66%	1.58[1.2,2.08]
Subtotal (95% CI)	**300**	**101**		**15.66%**	**1.58[1.2,2.08]**
Total events: 174 (Treatment), 37 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.29(P=0)					
1.4.2 Fluoxetine					
Dominguez 1991	76/266	7/89		4.21%	3.63[1.74,7.58]
Montgomery 1993c	75/160	15/57		8.6%	1.78[1.12,2.83]
Subtotal (95% CI)	**426**	**146**		**12.81%**	**2.41[1.18,4.91]**
Total events: 151 (Treatment), 22 (Control)					
Heterogeneity: Tau^2=0.17; Chi^2=2.76, df=1(P=0.1); I^2=63.72%					
Test for overall effect: Z=2.41(P=0.02)					
1.4.3 Fluvoxamine					
Goodman 1989	9/21	0/21		0.34%	19[1.18,306.79]
Goodman 1996	26/80	7/80		3.85%	3.71[1.71,8.06]
Hollander 2002	51/117	28/120		11%	1.87[1.27,2.74]
Nakajima 1996	31/81	6/44		3.7%	2.81[1.27,6.2]
Subtotal (95% CI)	**299**	**265**		**18.9%**	**2.68[1.58,4.56]**
Total events: 117 (Treatment), 41 (Control)					
Heterogeneity: Tau^2=0.12; Chi^2=5.45, df=3(P=0.14); I^2=44.92%					
Test for overall effect: Z=3.65(P=0)					
1.4.4 Paroxetine					
Kamijima 2004	47/94	22/93		9.93%	2.11[1.39,3.21]
Zohar 1996	109/201	35/99		14.64%	1.53[1.14,2.06]
Subtotal (95% CI)	**295**	**192**		**24.56%**	**1.74[1.28,2.36]**
Total events: 156 (Treatment), 57 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=1.51, df=1(P=0.22); I^2=33.99%					
Test for overall effect: Z=3.53(P=0)					
1.4.5 Sertraline					
Chouinard 1990	11/43	5/44		2.59%	2.25[0.85,5.94]
Greist 1992b	93/241	25/84		11.69%	1.3[0.9,1.87]
Kronig 1999	35/85	18/79		8.25%	1.81[1.12,2.92]
Ushijima 1997	23/56	10/41		5.54%	1.68[0.9,3.14]
Subtotal (95% CI)	**425**	**248**		**28.06%**	**1.54[1.2,1.99]**
Total events: 162 (Treatment), 58 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.95, df=3(P=0.58); I^2=0%					
Test for overall effect: Z=3.35(P=0)					
Total (95% CI)	**1745**	**952**		**100%**	**1.84[1.56,2.17]**
Total events: 760 (Treatment), 215 (Control)					
Heterogeneity: Tau^2=0.03; Chi^2=17.28, df=12(P=0.14); I^2=30.54%					
Test for overall effect: Z=7.29(P<0.0001)					
Test for subgroup differences: Not applicable					

Favours control — Favours treatment

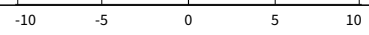
Analysis 1.5. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 5 YBOCS reduction (mean duration of OCD).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Mean duration of OCD 10 yrs or less							
Chouinard 1990	43	-3.8 (5.2)	44	-1.5 (5.2)		8.29%	-2.31[-4.5,-0.12]
Greist 1992b	240	-5.6 (6.2)	84	-3.4 (6.2)		16.87%	-2.17[-3.71,-0.63]
Nakajima 1996	60	-7.1 (7)	33	-1.9 (7.2)		4.34%	-5.2[-8.23,-2.17]
Ushijima 1997	56	17.7 (9)	41	19.7 (8.5)		3.24%	-1.97[-5.48,1.54]
Subtotal ***	**399**		**202**			**32.75%**	**-2.59[-3.69,-1.48]**
Heterogeneity: Tau^2=0; Chi^2=3.31, df=3(P=0.35); I^2=9.47%							
Test for overall effect: Z=4.59(P<0.0001)							
1.5.2 Mean duration of OCD more than 10 yrs							
Goodman 1989	21	19.4 (7)	21	28 (7)		2.23%	-8.6[-12.83,-4.37]
Goodman 1996	78	-3.9 (6.3)	78	-1.7 (4.9)		12.89%	-2.24[-4,-0.48]
Hollander 2002	117	-8.5 (7.6)	120	-5.6 (7.7)		10.52%	-2.9[-4.85,-0.95]
Jenike 1990b	10	20.6 (9.2)	9	22.3 (7.8)		0.68%	-1.7[-9.35,5.95]
Kamijima 2004	94	-8.1 (8)	94	-3.5 (6.1)		9.65%	-4.65[-6.68,-2.62]
Kasper 1999	300	-9.2 (7.1)	101	-5.6 (6.9)		16.26%	-3.63[-5.2,-2.06]
Kronig 1999	85	-8.5 (10.2)	79	-4.1 (10.2)		4.13%	-4.36[-7.47,-1.25]
Zohar 1996	198	-8 (8)	99	-5 (7.9)		10.9%	-3[-4.91,-1.09]
Subtotal ***	**903**		**601**			**67.25%**	**-3.48[-4.25,-2.71]**
Heterogeneity: Tau^2=0; Chi^2=9.93, df=7(P=0.19); I^2=29.5%							
Test for overall effect: Z=8.86(P<0.0001)							
Total ***	**1302**		**803**			**100%**	**-3.19[-3.82,-2.56]**
Heterogeneity: Tau^2=0; Chi^2=14.95, df=11(P=0.18); I^2=26.4%							
Test for overall effect: Z=9.9(P<0.0001)							
Test for subgroup differences: Chi^2=1.7, df=1 (P=0.19), I^2=41.28%							

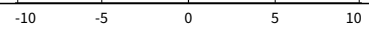


Analysis 1.6. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 6 YBOCS reduction (severe secondary depression).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.1 Studies with some pts with severe sec. depression							
Dominguez 1991	266	-5.4 (7.9)	89	-0.8 (5.7)		10.9%	-4.64[-6.15,-3.13]
Goodman 1989	21	19.4 (7)	21	28 (7)		2.22%	-8.6[-12.83,-4.37]
Goodman 1996	78	-3.9 (6.3)	78	-1.7 (4.9)		9.05%	-2.24[-4,-0.48]
Jenike 1990a	18	18.8 (4)	20	21.8 (7.6)		2.69%	-3[-6.81,0.81]
Kamijima 2004	94	-8.1 (8)	94	-3.5 (6.1)		7.44%	-4.65[-6.68,-2.62]
Montgomery 1993c	158	-5.3 (6.8)	56	-3.7 (6)		8.25%	-1.63[-3.52,0.26]
Zohar 1996	198	-8 (8)	99	-5 (7.9)		8.1%	-3[-4.91,-1.09]
Subtotal ***	**833**		**457**			**48.65%**	**-3.6[-4.89,-2.3]**
Heterogeneity: Tau^2=1.72; Chi^2=15.06, df=6(P=0.02); I^2=60.16%							
Test for overall effect: Z=5.43(P<0.0001)							

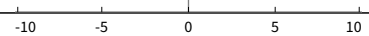


Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.6.2 Studies with no pts with severe sec. depression							
Chouinard 1990	43	-3.8 (5.2)	44	-1.5 (5.2)		6.67%	-2.31[-4.5,-0.12]
Greist 1992b	240	-5.6 (6.2)	84	-3.4 (6.2)		10.67%	-2.17[-3.71,-0.63]
Hollander 2002	117	-8.5 (7.6)	120	-5.6 (7.7)		7.91%	-2.9[-4.85,-0.95]
Hollander 2003	259	19.1 (8.9)	89	21.8 (7.1)		8.64%	-2.62[-4.44,-0.8]
Jenike 1990b	10	20.6 (9.2)	9	22.3 (7.8)		0.72%	-1.7[-9.35,5.95]
Jenike 1997	19	16.2 (6.3)	18	18.7 (6.1)		2.47%	-2.5[-6.5,1.5]
Kasper 1999	300	-9.2 (7.1)	101	-5.6 (6.9)		10.44%	-3.63[-5.2,-2.06]
Kronig 1999	85	-8.5 (10.2)	79	-4.1 (10.2)		3.83%	-4.36[-7.47,-1.25]
Subtotal ***	**1073**		**544**			**51.35%**	**-2.84[-3.59,-2.09]**
Heterogeneity: Tau^2=0; Chi^2=3.02, df=7(P=0.88); I^2=0%							
Test for overall effect: Z=7.43(P<0.0001)							
Total ***	**1906**		**1001**			**100%**	**-3.16[-3.83,-2.5]**
Heterogeneity: Tau^2=0.45; Chi^2=19.44, df=14(P=0.15); I^2=27.98%							
Test for overall effect: Z=9.39(P<0.0001)							
Test for subgroup differences: Chi^2=1.36, df=1 (P=0.24), I^2=26.39%							



Analysis 1.7. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 7 YBOCS reduction (duration of trial).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.7.1 Duration of trials less than 12 wks							
Chouinard 1990	43	-3.8 (5.2)	44	-1.5 (5.2)		5.97%	-2.31[-4.5,-0.12]
Goodman 1989	21	19.4 (7)	21	28 (7)		1.96%	-8.6[-12.83,-4.37]
Goodman 1996	78	-3.9 (6.3)	78	-1.7 (4.9)		8.15%	-2.24[-4,-0.48]
Jenike 1990a	18	18.8 (4)	20	21.8 (7.6)		2.37%	-3[-6.81,0.81]
Jenike 1990b	10	20.6 (9.2)	9	22.3 (7.8)		0.64%	-1.7[-9.35,5.95]
Jenike 1997	19	16.2 (6.3)	18	18.7 (6.1)		2.18%	-2.5[-6.5,1.5]
Montgomery 1993c	158	-5.3 (6.8)	56	-3.7 (6)		7.42%	-1.63[-3.52,0.26]
Nakajima 1996	60	-7.1 (7)	33	-1.9 (7.2)		3.54%	-5.2[-8.23,-2.17]
Ushijima 1997	56	17.7 (9)	41	19.7 (8.5)		2.75%	-1.97[-5.48,1.54]
Subtotal ***	**463**		**320**			**34.96%**	**-2.92[-4.13,-1.72]**
Heterogeneity: Tau^2=1.04; Chi^2=11.95, df=8(P=0.15); I^2=33.08%							
Test for overall effect: Z=4.76(P<0.0001)							
1.7.2 Duration of trials 12 to 13 wks							
Dominguez 1991	266	-5.4 (7.9)	89	-0.8 (5.7)		9.88%	-4.64[-6.15,-3.13]
Greist 1992b	240	-5.6 (6.2)	84	-3.4 (6.2)		9.66%	-2.17[-3.71,-0.63]
Hollander 2002	117	-8.5 (0.5)	120	-5.6 (7.7)		10.93%	-2.9[-4.28,-1.52]
Hollander 2003	259	19.1 (8.9)	89	21.8 (7.1)		7.78%	-2.62[-4.44,-0.8]
Kamijima 2004	94	-8.1 (8)	94	-3.5 (6.1)		6.67%	-4.65[-6.68,-2.62]
Kasper 1999	300	-9.2 (7.1)	101	-5.6 (6.9)		9.45%	-3.63[-5.2,-2.06]
Kronig 1999	85	-8.5 (10.2)	79	-4.1 (10.2)		3.39%	-4.36[-7.47,-1.25]
Zohar 1996	198	-8 (8)	99	-5 (7.9)		7.27%	-3[-4.91,-1.09]
Subtotal ***	**1559**		**755**			**65.04%**	**-3.38[-4.05,-2.71]**
Heterogeneity: Tau^2=0.15; Chi^2=8.31, df=7(P=0.31); I^2=15.79%							



Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=9.9(P<0.0001)							
Total ***	**2022**		**1075**			**100%**	**-3.19[-3.81,-2.57]**
Heterogeneity: Tau²=0.41; Chi²=21.69, df=16(P=0.15); I²=26.23%							
Test for overall effect: Z=10.13(P<0.0001)							
Test for subgroup differences: Chi²=1.42, df=1 (P=0.23), I²=29.66%							

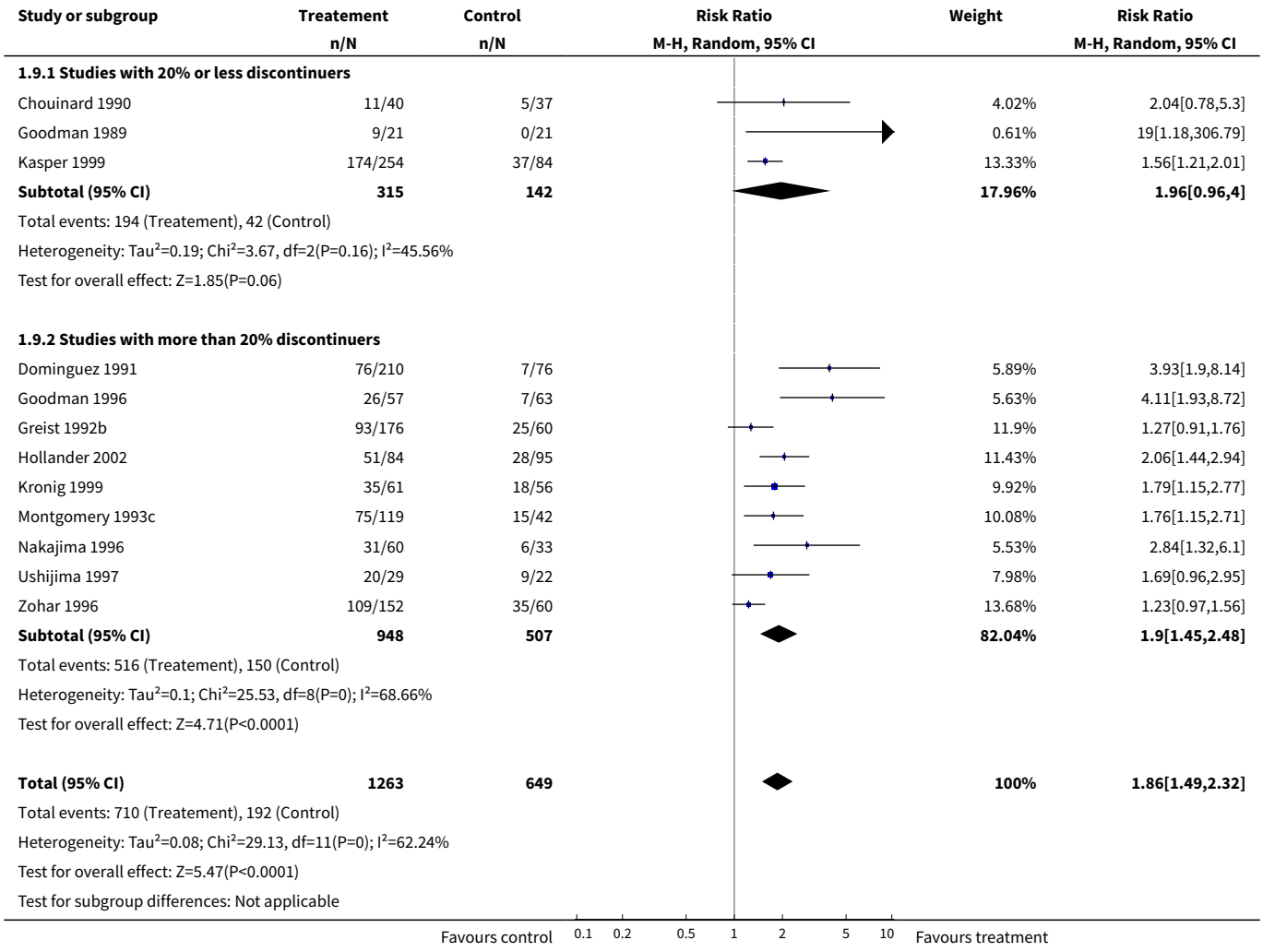
Favours treatment -10 -5 0 5 10 Favours control

Analysis 1.8. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 8 YBOCS reduction (proportion of discontinuers).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.8.1 Studies with 20% or less discontinuers							
Chouinard 1990	43	-3.8 (5.2)	44	-1.5 (5.2)		6.22%	-2.31[-4.5,-0.12]
Goodman 1989	21	19.4 (7)	21	28 (7)		2.06%	-8.6[-12.83,-4.37]
Hollander 2003	259	19.1 (8.9)	89	21.8 (7.1)		8.07%	-2.62[-4.44,-0.8]
Jenike 1990a	18	18.8 (4)	20	21.8 (7.6)		2.49%	-3[-6.81,0.81]
Jenike 1990b	10	20.6 (9.2)	9	22.3 (7.8)		0.67%	-1.7[-9.35,5.95]
Jenike 1997	19	16.2 (6.3)	18	18.7 (6.1)		2.29%	-2.5[-6.5,1.5]
Kasper 1999	300	-9.2 (7.1)	101	-5.6 (6.9)		9.78%	-3.63[-5.2,-2.06]
Subtotal ***	**670**		**302**			**31.58%**	**-3.27[-4.45,-2.1]**
Heterogeneity: Tau²=0.57; Chi²=7.83, df=6(P=0.25); I²=23.38%							
Test for overall effect: Z=5.45(P<0.0001)							
1.8.2 Studies with more than 20% discontinuers							
Dominguez 1991	266	-5.4 (7.9)	89	-0.8 (5.7)		10.21%	-4.64[-6.15,-3.13]
Goodman 1996	78	-3.9 (6.3)	78	-1.7 (4.9)		8.46%	-2.24[-4,-0.48]
Greist 1992b	240	-5.6 (6.2)	84	-3.4 (6.2)		9.99%	-2.17[-3.71,-0.63]
Hollander 2002	117	-8.5 (7.6)	120	-5.6 (7.7)		7.38%	-2.9[-4.85,-0.95]
Kamijima 2004	94	-8.1 (8)	94	-3.5 (6.1)		6.95%	-4.65[-6.68,-2.62]
Kronig 1999	85	-8.5 (10.2)	79	-4.1 (10.2)		3.56%	-4.36[-7.47,-1.25]
Montgomery 1993c	158	-5.3 (6.8)	56	-3.7 (6)		7.71%	-1.63[-3.52,0.26]
Nakajima 1996	60	-7.1 (7)	33	-1.9 (7.2)		3.71%	-5.2[-8.23,-2.17]
Ushijima 1997	56	17.7 (9)	41	19.7 (8.5)		2.88%	-1.97[-5.48,1.54]
Zohar 1996	198	-8 (8)	99	-5 (7.9)		7.56%	-3[-4.91,-1.09]
Subtotal ***	**1352**		**773**			**68.42%**	**-3.18[-3.98,-2.38]**
Heterogeneity: Tau²=0.56; Chi²=13.77, df=9(P=0.13); I²=34.63%							
Test for overall effect: Z=7.78(P<0.0001)							
Total ***	**2022**		**1075**			**100%**	**-3.21[-3.84,-2.57]**
Heterogeneity: Tau²=0.44; Chi²=21.61, df=16(P=0.16); I²=25.97%							
Test for overall effect: Z=9.89(P<0.0001)							
Test for subgroup differences: Chi²=0.01, df=1 (P=0.9), I²=0%							

Favours treatment -10 -5 0 5 10 Favours control

Analysis 1.9. Comparison 1 SSRIs versus Placebo - efficacy using YBOCS, Outcome 9 Responders per completers (proportion of discontinuers).



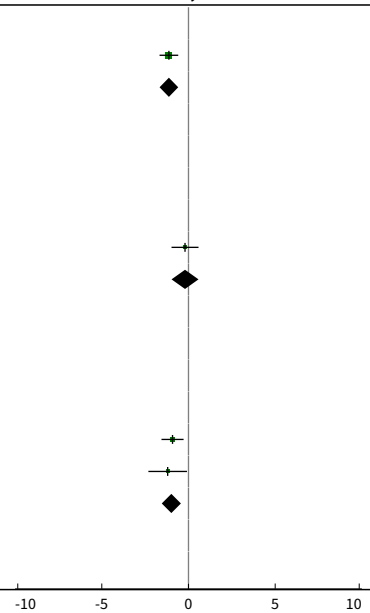
Comparison 2. SSRIs versus placebo - efficacy using NIMH-OC scale or other measures (individual SSRI drugs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SSRI versus placebo -efficacy using NIMH-OCS only	8	1359	Mean Difference (IV, Random, 95% CI)	-0.89 [-1.13, -0.64]
1.1 Cipramil	1	401	Mean Difference (IV, Random, 95% CI)	-1.13 [-1.67, -0.59]
1.2 Fluoxetine	1	37	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.98, 0.58]
1.3 Fluvoxamine	2	194	Mean Difference (IV, Random, 95% CI)	-0.99 [-1.54, -0.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Paroxetine	1	297	Mean Difference (IV, Random, 95% CI)	-1.1 [-1.80, -0.40]
1.5 Sertraline	3	430	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.22, -0.40]
2 SSRI v. placebo on NIMH-OCS or other scales (CGI -S for Montgomery 93 & Dominguez 91, & CGI-I Hollander 03)	11	2165	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.52, -0.33]
2.1 Cipramil	1	401	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.67, -0.21]
2.2 Fluoxetine	3	606	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.80, 0.08]
2.3 Fluvoxamine	3	431	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.61, -0.23]
2.4 Paroxetine	1	297	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.62, -0.14]
2.5 Sertraline	3	430	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.62, -0.20]

Analysis 2.1. Comparison 2 SSRIs versus placebo - efficacy using NIMH-OC scale or other measures (individual SSRI drugs), Outcome 1 SSRI versus placebo -efficacy using NIMH-OCS only.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.1.1 Cipramil							
Kasper 1999	300	-2.9 (2.6)	101	-1.8 (2.3)		21.1%	-1.13[-1.67,-0.59]
Subtotal ***	**300**		**101**			**21.1%**	**-1.13[-1.67,-0.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.11(P<0.0001)							
2.1.2 Fluoxetine							
Jenike 1997	19	7 (1.1)	18	7.2 (1.3)		10.1%	-0.2[-0.98,0.58]
Subtotal ***	**19**		**18**			**10.1%**	**-0.2[-0.98,0.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.5(P=0.61)							
2.1.3 Fluvoxamine							
Goodman 1996	78	-1.3 (2.3)	78	-0.4 (1.8)		15.08%	-0.92[-1.56,-0.28]
Jenike 1990a	18	6.8 (1.2)	20	8 (2.2)		4.94%	-1.2[-2.31,-0.09]
Subtotal ***	**96**		**98**			**20.02%**	**-0.99[-1.54,-0.44]**
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%							
Test for overall effect: Z=3.51(P=0)							



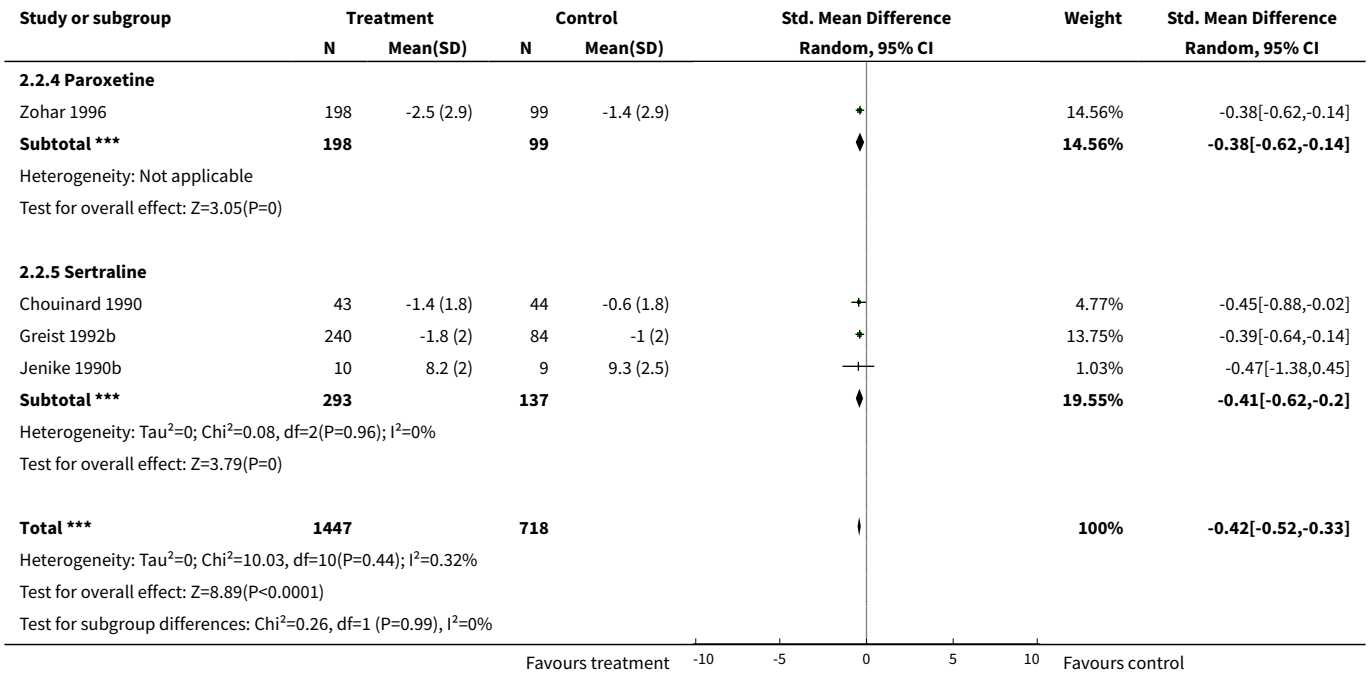
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.1.4 Paroxetine							
Zohar 1996	198	-2.5 (2.9)	99	-1.4 (2.9)		12.49%	-1.1[-1.8,-0.4]
Subtotal ***	**198**		**99**			**12.49%**	**-1.1[-1.8,-0.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.08(P=0)							
2.1.5 Sertraline							
Chouinard 1990	43	-1.4 (1.8)	44	-0.6 (1.8)		10.33%	-0.83[-1.6,-0.06]
Greist 1992b	240	-1.8 (2)	84	-1 (2)		24.51%	-0.78[-1.28,-0.28]
Jenike 1990b	10	8.2 (2)	9	9.3 (2.5)		1.45%	-1.1[-3.15,0.95]
Subtotal ***	**293**		**137**			**36.3%**	**-0.81[-1.22,-0.4]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=2(P=0.95); I^2=0%							
Test for overall effect: Z=3.85(P=0)							
Total ***	**906**		**453**			**100%**	**-0.89[-1.13,-0.64]**
Heterogeneity: Tau^2=0; Chi^2=4.69, df=7(P=0.7); I^2=0%							
Test for overall effect: Z=7.03(P<0.0001)							
Test for subgroup differences: Chi^2=4.41, df=1 (P=0.35), I^2=9.32%							

Favours treatment -10 -5 0 5 10 Favours control

Analysis 2.2. Comparison 2 SSRIs versus placebo - efficacy using NIMH-OC scale or other measures (individual SSRI drugs), Outcome 2 SSRI v. placebo on NIMH-OCS or other scales (CGI -S for Montgomery 93 & Dominguez 91, & CGI-I Hollander 03).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
2.2.1 Cipramil							
Kasper 1999	300	-2.9 (2.6)	101	-1.8 (2.3)		16.62%	-0.44[-0.67,-0.21]
Subtotal ***	**300**		**101**			**16.62%**	**-0.44[-0.67,-0.21]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=3.81(P=0)							
2.2.2 Fluoxetine							
Dominguez 1991	266	-0.9 (1.3)	89	-0 (1)		14.29%	-0.7[-0.94,-0.45]
Jenike 1997	19	7 (1.1)	18	7.2 (1.3)		2.07%	-0.16[-0.81,0.48]
Montgomery 1993c	158	-0.8 (1.1)	56	-0.7 (1)		9.27%	-0.13[-0.43,0.18]
Subtotal ***	**443**		**163**			**25.64%**	**-0.36[-0.8,0.08]**
Heterogeneity: Tau^2=0.11; Chi^2=8.98, df=2(P=0.01); I^2=77.73%							
Test for overall effect: Z=1.62(P=0.11)							
2.2.3 Fluvoxamine							
Goodman 1996	78	-1.3 (2.3)	78	-0.4 (1.8)		8.54%	-0.45[-0.77,-0.13]
Hollander 2002	117	-1 (1.1)	120	-0.6 (1.1)		13.07%	-0.36[-0.62,-0.11]
Jenike 1990a	18	6.8 (1.2)	20	8 (2.2)		2.01%	-0.65[-1.31,0]
Subtotal ***	**213**		**218**			**23.63%**	**-0.42[-0.61,-0.23]**
Heterogeneity: Tau^2=0; Chi^2=0.72, df=2(P=0.7); I^2=0%							
Test for overall effect: Z=4.3(P<0.0001)							

Favours treatment -10 -5 0 5 10 Favours control



Comparison 3. SSRIs versus Placebo - adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Citalopram - overall adverse effects	1	401	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.02, 1.45]
2 Citalopram - nausea, headache and insomnia	1	1203	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.96, 3.13]
2.1 Nausea	1	401	Risk Ratio (M-H, Random, 95% CI)	2.47 [1.28, 4.77]
2.2 Headache	1	401	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.63, 1.76]
2.3 Insomnia	1	401	Risk Ratio (M-H, Random, 95% CI)	2.26 [1.06, 4.84]
3 Citalopram - sexual side effects	1	401	Risk Ratio (M-H, Random, 95% CI)	18.64 [1.15, 302.80]
4 Fluoxetine - nausea, headache, insomnia and anxiety	2	1921	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.93, 1.49]
4.1 Nausea	2	569	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.44, 3.25]
4.2 Headache	2	569	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.79, 1.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 Insomnia	2	569	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.83, 1.68]
4.4 Anxiety	1	214	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.56, 3.60]
5 Fluvoxamine - overall adverse effects	3	446	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.07, 1.21]
6 Fluvoxamine - insomnia, nausea, fatigue, headache, somnolence and asthenia	3	1944	Risk Ratio (M-H, Random, 95% CI)	2.07 [1.62, 2.65]
6.1 Insomnia	3	446	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.26, 2.60]
6.2 Nausea	3	446	Risk Ratio (M-H, Random, 95% CI)	2.64 [1.75, 3.98]
6.3 Fatigue	1	38	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.51, 6.67]
6.4 Headache	2	198	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.38, 2.41]
6.5 Somnolence	2	408	Risk Ratio (M-H, Random, 95% CI)	2.46 [1.59, 3.79]
6.6 Asthenia	2	408	Risk Ratio (M-H, Random, 95% CI)	2.83 [1.74, 4.60]
7 Fluvoxamine - sexual side effects	3	446	Risk Ratio (M-H, Random, 95% CI)	4.02 [1.85, 8.73]
8 Paroxetine - overall adverse effects	2	489	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.91, 1.42]
9 Paroxetine - asthenia, headache, insomnia, somnolence, nausea and constipation	3	2511	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.17, 2.36]
9.1 Asthenia	1	300	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.90, 2.34]
9.2 Headache	2	648	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.53, 1.69]
9.3 Insomnia	2	648	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.15, 2.53]
9.4 Somnolence	2	537	Risk Ratio (M-H, Random, 95% CI)	1.85 [1.12, 3.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.5 Nausea	1	189	Risk Ratio (M-H, Random, 95% CI)	3.96 [1.82, 8.61]
9.6 Constipation	1	189	Risk Ratio (M-H, Random, 95% CI)	4.29 [1.26, 14.56]
10 Paroxetine - sexual adverse effects	1	189	Risk Ratio (M-H, Random, 95% CI)	6.93 [0.36, 132.29]
11 Sertraline - overall adverse effects	4	598	Risk Ratio (M-H, Random, 95% CI)	1.21 [1.08, 1.37]
12 Sertraline - nausea, insomnia, dyspepsia, constipation, sedation, forgetfulness, headache and diarrhoea	4	3148	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.40, 2.51]
12.1 Nausea	4	598	Risk Ratio (M-H, Random, 95% CI)	2.60 [0.89, 7.63]
12.2 Insomnia	3	579	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.09, 4.56]
12.3 Dyspepsia	2	412	Risk Ratio (M-H, Random, 95% CI)	4.40 [0.32, 59.74]
12.4 Constipation	1	19	Risk Ratio (M-H, Random, 95% CI)	2.7 [0.34, 21.53]
12.5 Sedation	3	511	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.65, 2.62]
12.6 Forgetfulness	1	19	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.12, 59.57]
12.7 Headache	3	431	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.74, 2.03]
12.8 Diarrhoea	3	579	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.11, 4.23]
13 Sertraline - sexual side effects	4	598	Risk Ratio (M-H, Random, 95% CI)	5.74 [0.68, 48.31]

Analysis 3.1. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 1 Citalopram - overall adverse effects.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kasper 1999	213/300	59/101		100%	1.22[1.02,1.45]
Total (95% CI)	**300**	**101**		**100%**	**1.22[1.02,1.45]**

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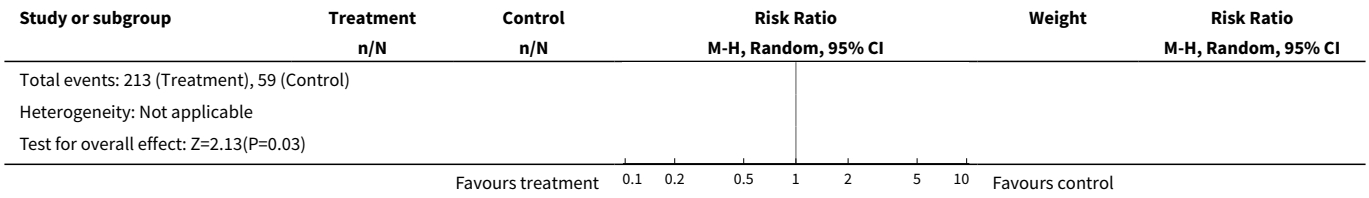
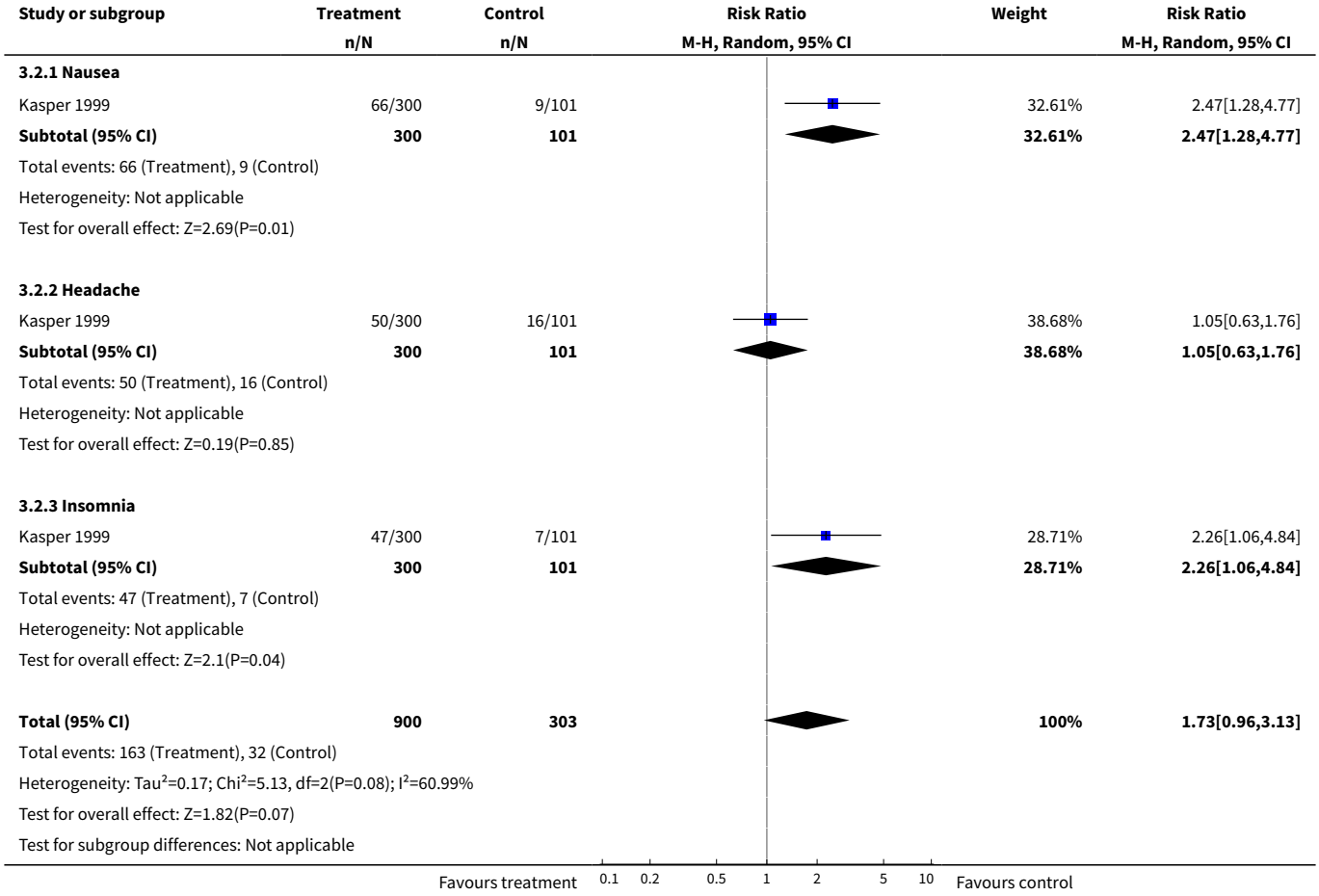
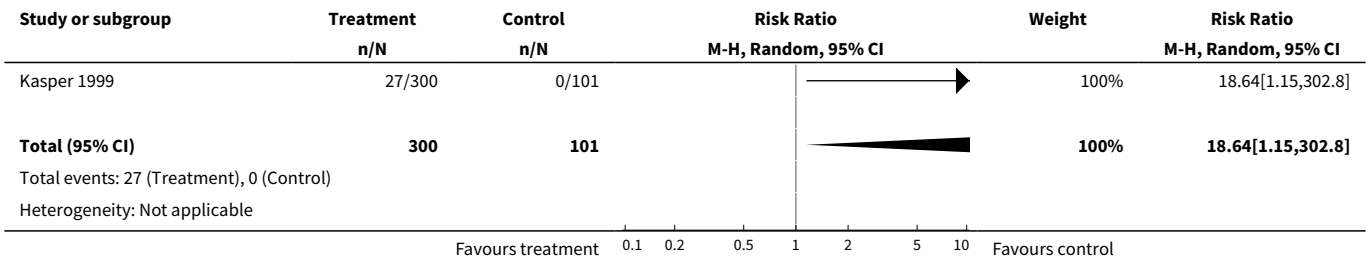


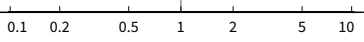
Analysis 3.2. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 2 Citalopram - nausea, headache and insomnia.



Analysis 3.3. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 3 Citalopram - sexual side effects.

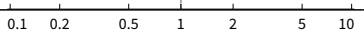


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.06(P=0.04)					



Analysis 3.4. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 4 Fluoxetine - nausea, headache, insomnia and anxiety.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.4.1 Nausea					
Dominguez 1991	70/266	12/89		14.35%	1.95[1.11,3.43]
Montgomery 1993c	22/158	11/56		11.1%	0.71[0.37,1.37]
Subtotal (95% CI)	**424**	**145**		**25.45%**	**1.19[0.44,3.25]**
Total events: 92 (Treatment), 23 (Control)					
Heterogeneity: Tau^2=0.43; Chi^2=5.37, df=1(P=0.02); I^2=81.37%					
Test for overall effect: Z=0.35(P=0.73)					
3.4.2 Headache					
Dominguez 1991	78/266	21/89		22.69%	1.24[0.82,1.89]
Montgomery 1993c	27/158	11/56		11.87%	0.87[0.46,1.64]
Subtotal (95% CI)	**424**	**145**		**34.56%**	**1.11[0.79,1.58]**
Total events: 105 (Treatment), 32 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
3.4.3 Insomnia					
Dominguez 1991	79/266	20/89		21.93%	1.32[0.86,2.03]
Montgomery 1993c	29/158	11/56		12.12%	0.93[0.5,1.74]
Subtotal (95% CI)	**424**	**145**		**34.05%**	**1.18[0.83,1.68]**
Total events: 108 (Treatment), 31 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					
3.4.4 Anxiety					
Montgomery 1993c	20/158	5/56		5.94%	1.42[0.56,3.6]
Subtotal (95% CI)	**158**	**56**		**5.94%**	**1.42[0.56,3.6]**
Total events: 20 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.46)					
Total (95% CI)	**1430**	**491**		**100%**	**1.18[0.93,1.49]**
Total events: 325 (Treatment), 91 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=7.34, df=6(P=0.29); I^2=18.26%					
Test for overall effect: Z=1.36(P=0.17)					
Test for subgroup differences: Not applicable					

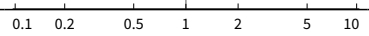


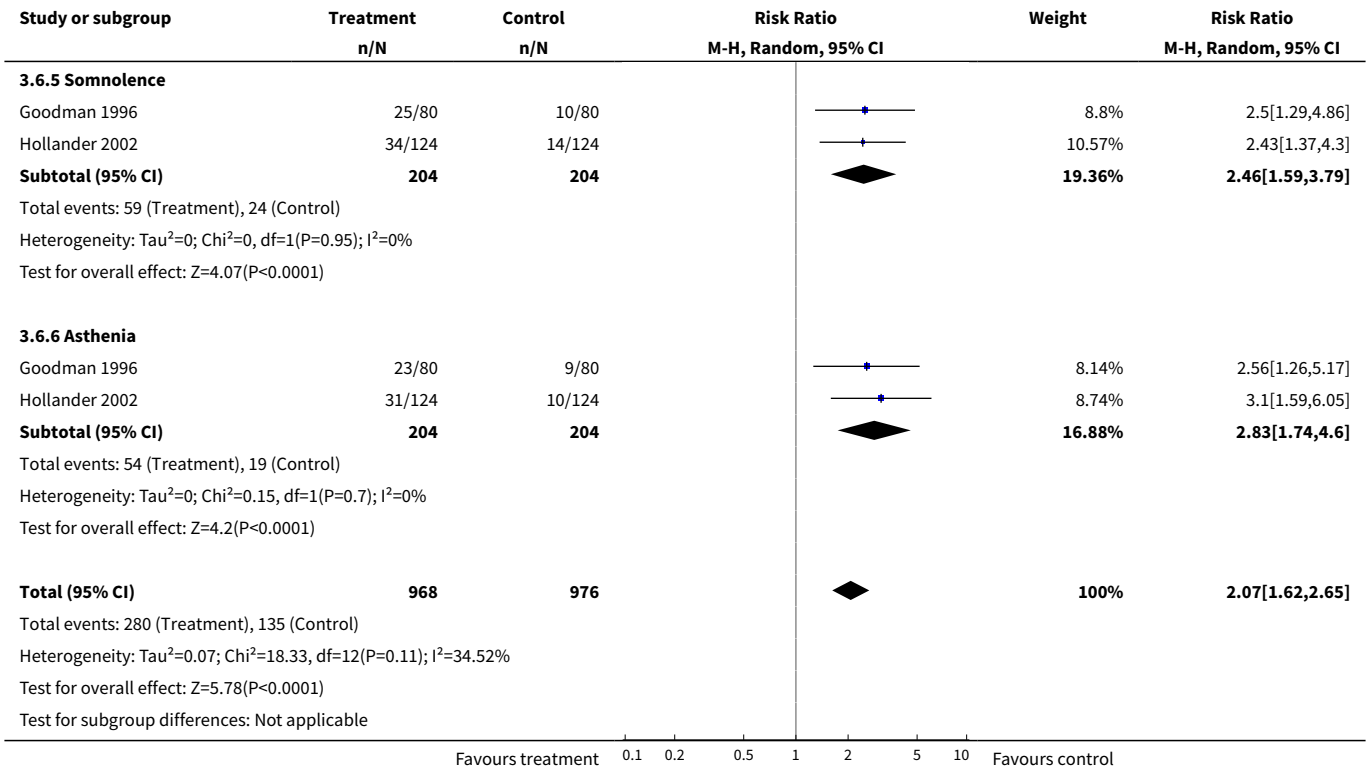
Analysis 3.5. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 5 Fluvoxamine - overall adverse effects.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Goodman 1996	76/80	67/80		33.64%	1.13[1.02,1.26]
Hollander 2002	120/124	106/124		63.3%	1.13[1.05,1.23]
Jenike 1990a	16/18	13/20		3.06%	1.37[0.95,1.96]
Total (95% CI)	**222**	**224**		**100%**	**1.14[1.07,1.21]**
Total events: 212 (Treatment), 186 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.08, df=2(P=0.58); I^2=0%					
Test for overall effect: Z=4.05(P<0.0001)					

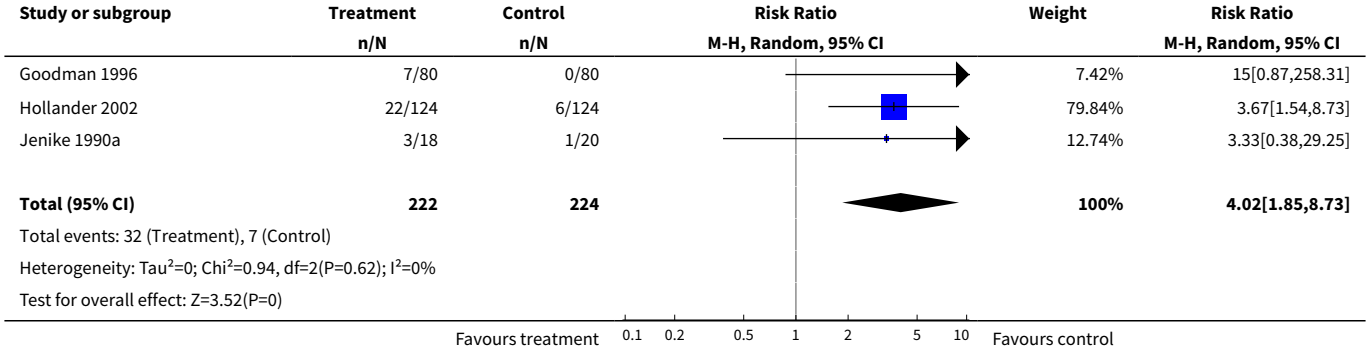
Analysis 3.6. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 6 Fluvoxamine - insomnia, nausea, fatigue, headache, somnolence and asthenia.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Insomnia					
Goodman 1996	26/80	15/80		10.9%	1.73[1,3.02]
Hollander 2002	43/124	25/124		14.09%	1.72[1.12,2.63]
Jenike 1990a	7/18	1/20		1.44%	7.78[1.06,57.25]
Subtotal (95% CI)	**222**	**224**		**26.43%**	**1.81[1.26,2.6]**
Total events: 76 (Treatment), 41 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=2.17, df=2(P=0.34); I^2=7.91%					
Test for overall effect: Z=3.23(P=0)					
3.6.2 Nausea					
Goodman 1996	21/80	8/80		7.45%	2.63[1.24,5.57]
Hollander 2002	42/124	16/124		11.7%	2.63[1.56,4.41]
Jenike 1990a	5/18	2/20		2.41%	2.78[0.61,12.59]
Subtotal (95% CI)	**222**	**224**		**21.55%**	**2.64[1.75,3.98]**
Total events: 68 (Treatment), 26 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=2(P=1); I^2=0%					
Test for overall effect: Z=4.62(P<0.0001)					
3.6.3 Fatigue					
Jenike 1990a	5/18	3/20		3.22%	1.85[0.51,6.67]
Subtotal (95% CI)	**18**	**20**		**3.22%**	**1.85[0.51,6.67]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.94(P=0.35)					
3.6.4 Headache					
Goodman 1996	13/80	19/80		9.34%	0.68[0.36,1.29]
Jenike 1990a	5/18	3/20		3.22%	1.85[0.51,6.67]
Subtotal (95% CI)	**98**	**100**		**12.56%**	**0.96[0.38,2.41]**
Total events: 18 (Treatment), 22 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=1.86, df=1(P=0.17); I^2=46.31%					
Test for overall effect: Z=0.09(P=0.93)					

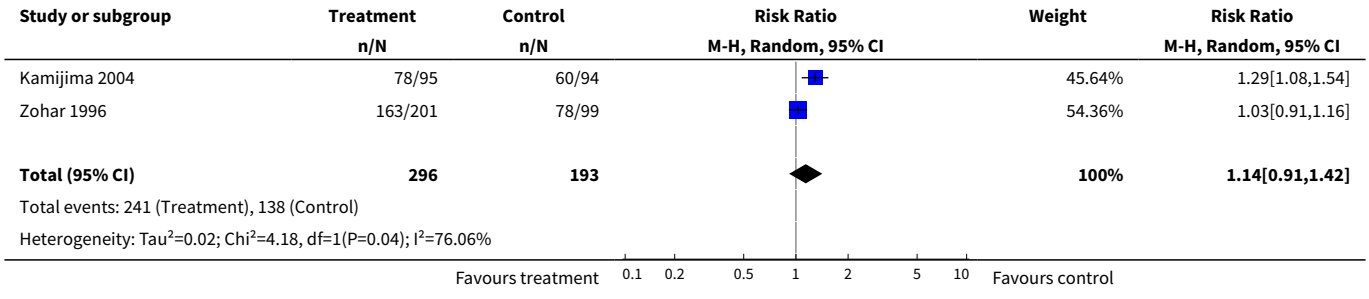




Analysis 3.7. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 7 Fluvoxamine - sexual side effects.



Analysis 3.8. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 8 Paroxetine - overall adverse effects.



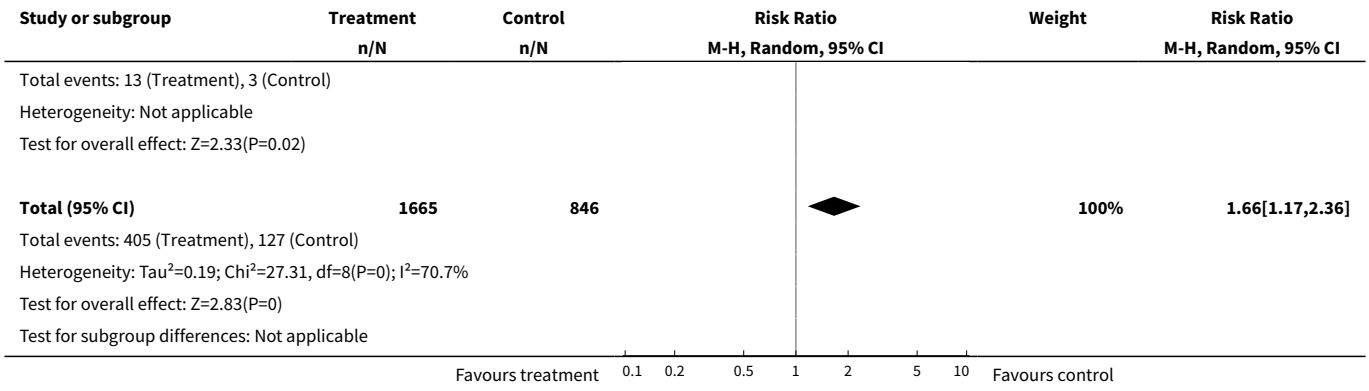
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.16(P=0.25)					

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

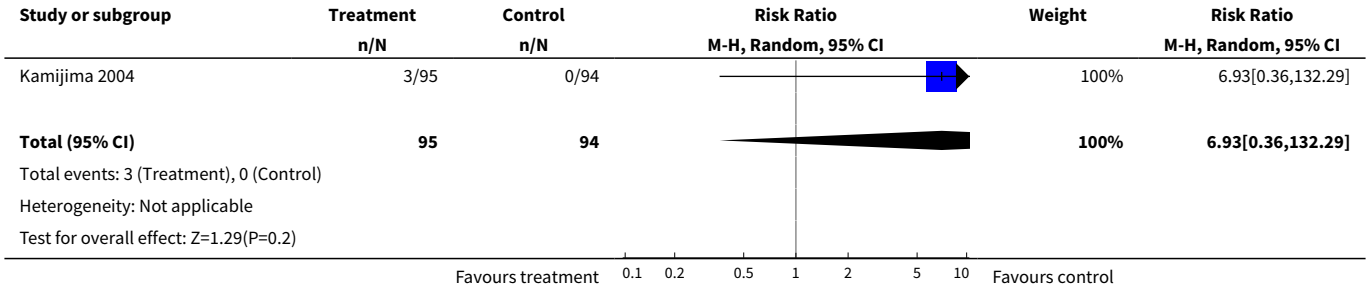
Analysis 3.9. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 9 Paroxetine - asthenia, headache, insomnia, somnolence, nausea and constipation.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Asthenia					
Zohar 1996	53/201	18/99		12.74%	1.45[0.9,2.34]
Subtotal (95% CI)	**201**	**99**		**12.74%**	**1.45[0.9,2.34]**
Total events: 53 (Treatment), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.13)					
3.9.2 Headache					
Hollander 2003	61/259	29/89		14.05%	0.72[0.5,1.05]
Zohar 1996	50/201	19/99		12.83%	1.3[0.81,2.07]
Subtotal (95% CI)	**460**	**188**		**26.88%**	**0.95[0.53,1.69]**
Total events: 111 (Treatment), 48 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=3.71, df=1(P=0.05); I^2=73.02%					
Test for overall effect: Z=0.17(P=0.86)					
3.9.3 Insomnia					
Hollander 2003	59/259	11/89		11.25%	1.84[1.01,3.35]
Zohar 1996	49/201	15/99		12.13%	1.61[0.95,2.72]
Subtotal (95% CI)	**460**	**188**		**23.38%**	**1.71[1.15,2.53]**
Total events: 108 (Treatment), 26 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%					
Test for overall effect: Z=2.66(P=0.01)					
3.9.4 Somnolence					
Hollander 2003	70/259	10/89		11%	2.41[1.3,4.46]
Kamijima 2004	22/95	15/94		11.32%	1.45[0.8,2.62]
Subtotal (95% CI)	**354**	**183**		**22.32%**	**1.85[1.12,3.06]**
Total events: 92 (Treatment), 25 (Control)					
Heterogeneity: Tau^2=0.04; Chi^2=1.38, df=1(P=0.24); I^2=27.44%					
Test for overall effect: Z=2.41(P=0.02)					
3.9.5 Nausea					
Kamijima 2004	28/95	7/94		9.17%	3.96[1.82,8.61]
Subtotal (95% CI)	**95**	**94**		**9.17%**	**3.96[1.82,8.61]**
Total events: 28 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.47(P=0)					
3.9.6 Constipation					
Kamijima 2004	13/95	3/94		5.52%	4.29[1.26,14.56]
Subtotal (95% CI)	**95**	**94**		**5.52%**	**4.29[1.26,14.56]**

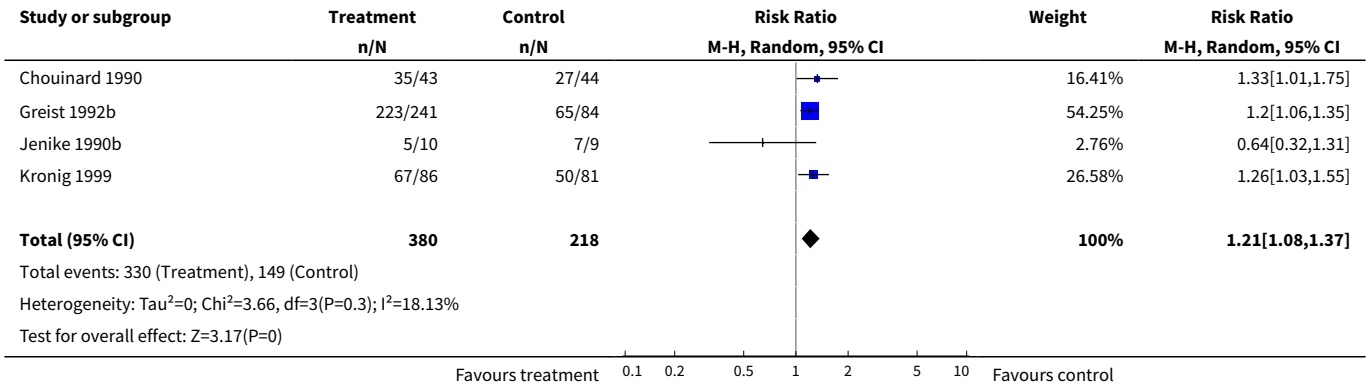
Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control



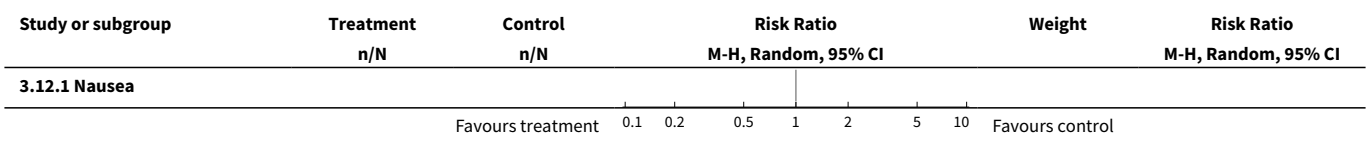
Analysis 3.10. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 10 Paroxetine - sexual adverse effects.

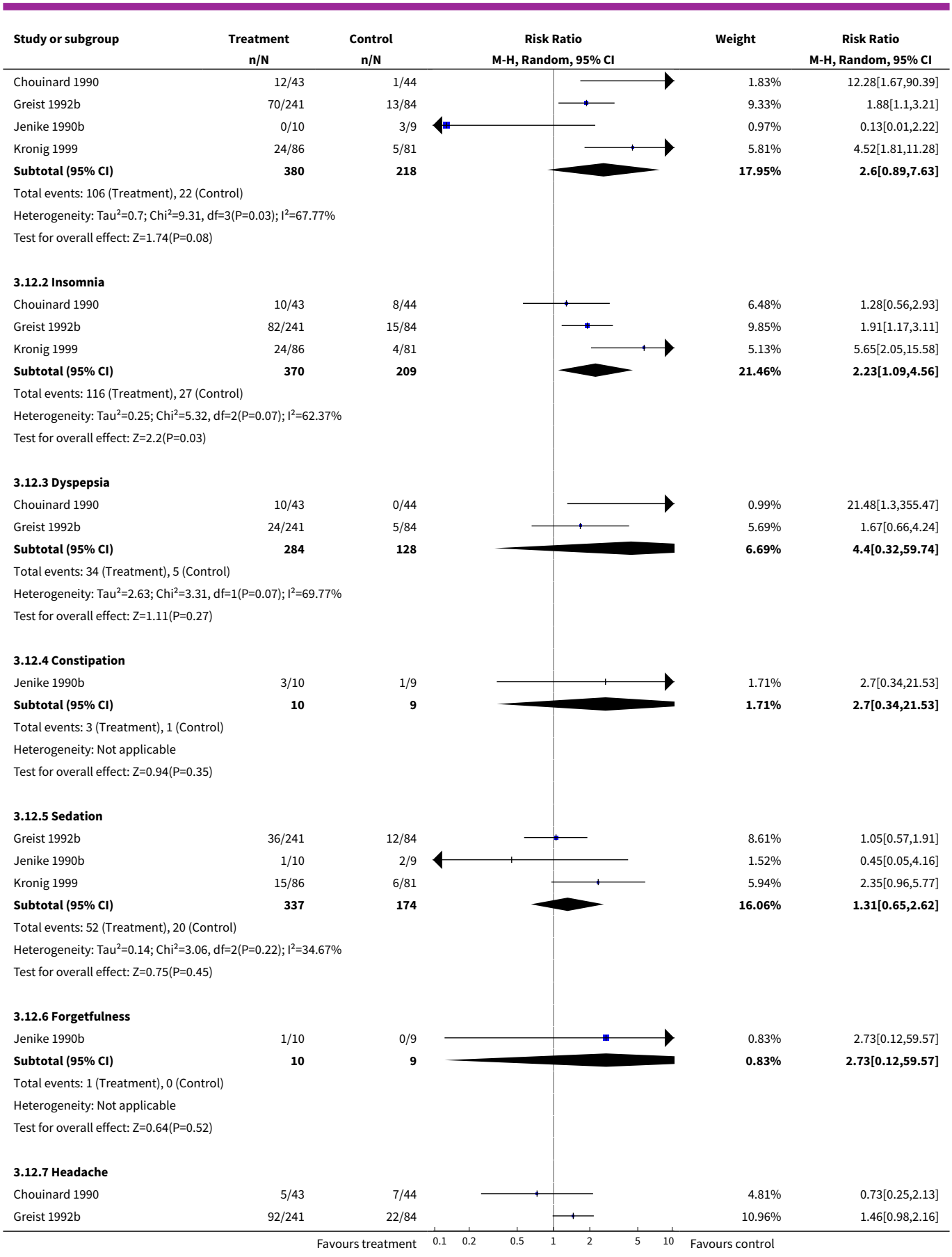


Analysis 3.11. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 11 Sertraline - overall adverse effects.

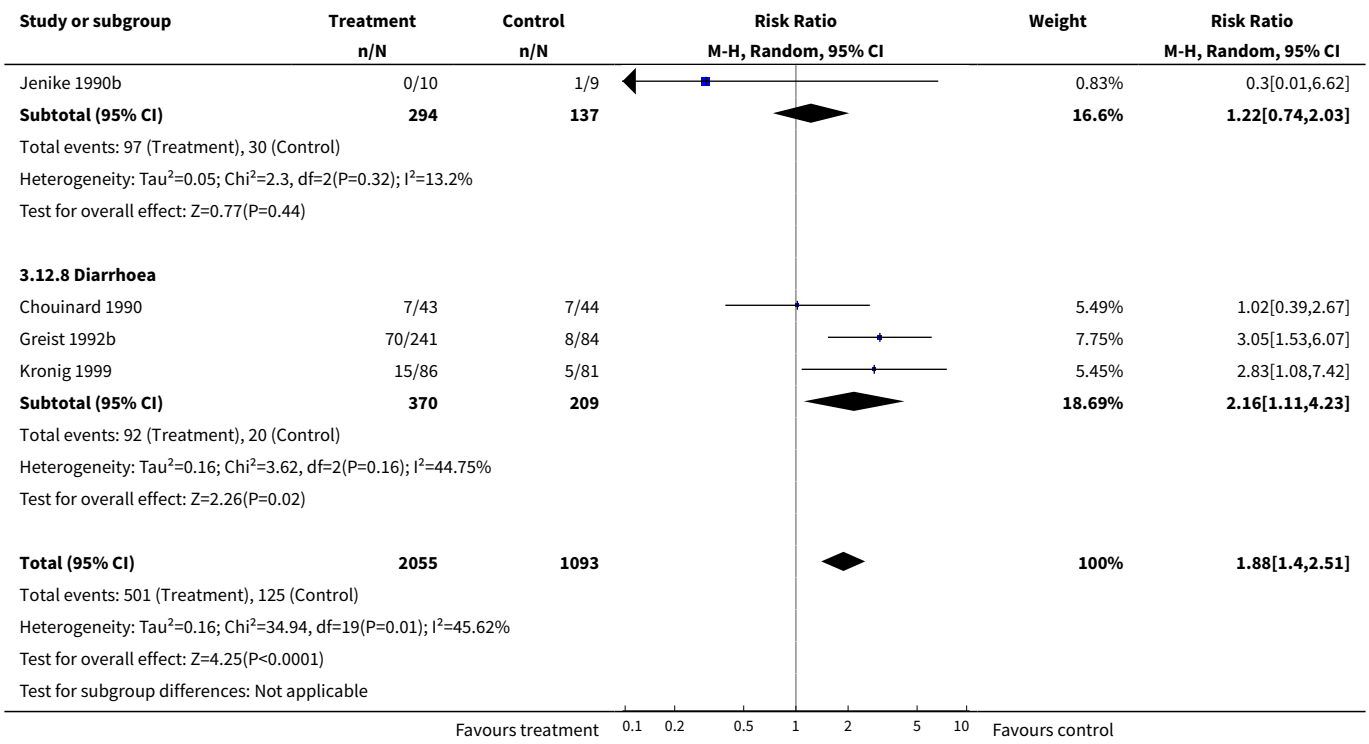


Analysis 3.12. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 12 Sertraline - nausea, insomnia, dyspepsia, constipation, sedation, forgetfulness, headache and diarrhoea.

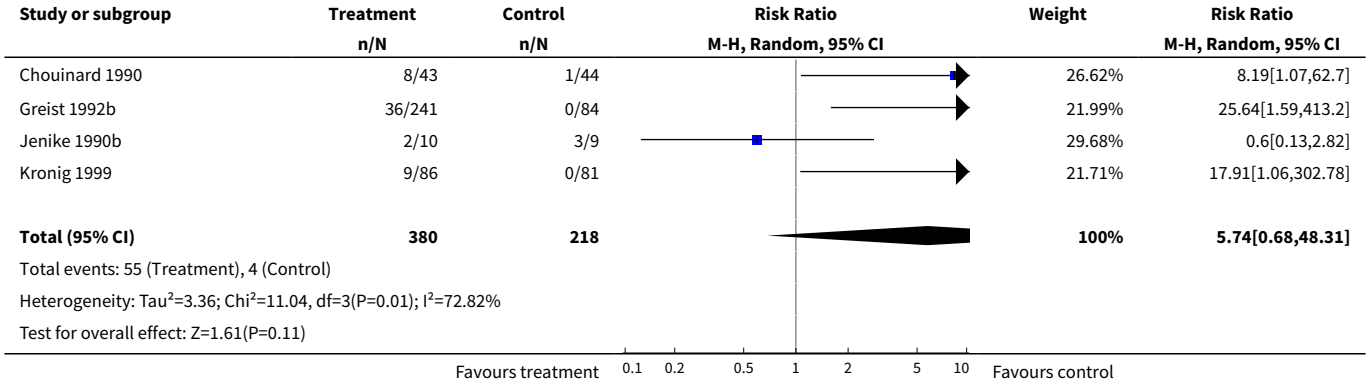




Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Chouinard 1990	12/43	1/44		1.83%	12.28[1.67,90.39]
Greist 1992b	70/241	13/84		9.33%	1.88[1.1,3.21]
Jenike 1990b	0/10	3/9		0.97%	0.13[0.01,2.22]
Kronig 1999	24/86	5/81		5.81%	4.52[1.81,11.28]
Subtotal (95% CI)	**380**	**218**		**17.95%**	**2.6[0.89,7.63]**
Total events: 106 (Treatment), 22 (Control)					
Heterogeneity: Tau²=0.7; Chi²=9.31, df=3(P=0.03); I²=67.77%					
Test for overall effect: Z=1.74(P=0.08)					
3.12.2 Insomnia					
Chouinard 1990	10/43	8/44		6.48%	1.28[0.56,2.93]
Greist 1992b	82/241	15/84		9.85%	1.91[1.17,3.11]
Kronig 1999	24/86	4/81		5.13%	5.65[2.05,15.58]
Subtotal (95% CI)	**370**	**209**		**21.46%**	**2.23[1.09,4.56]**
Total events: 116 (Treatment), 27 (Control)					
Heterogeneity: Tau²=0.25; Chi²=5.32, df=2(P=0.07); I²=62.37%					
Test for overall effect: Z=2.2(P=0.03)					
3.12.3 Dyspepsia					
Chouinard 1990	10/43	0/44		0.99%	21.48[1.3,355.47]
Greist 1992b	24/241	5/84		5.69%	1.67[0.66,4.24]
Subtotal (95% CI)	**284**	**128**		**6.69%**	**4.4[0.32,59.74]**
Total events: 34 (Treatment), 5 (Control)					
Heterogeneity: Tau²=2.63; Chi²=3.31, df=1(P=0.07); I²=69.77%					
Test for overall effect: Z=1.11(P=0.27)					
3.12.4 Constipation					
Jenike 1990b	3/10	1/9		1.71%	2.7[0.34,21.53]
Subtotal (95% CI)	**10**	**9**		**1.71%**	**2.7[0.34,21.53]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.94(P=0.35)					
3.12.5 Sedation					
Greist 1992b	36/241	12/84		8.61%	1.05[0.57,1.91]
Jenike 1990b	1/10	2/9		1.52%	0.45[0.05,4.16]
Kronig 1999	15/86	6/81		5.94%	2.35[0.96,5.77]
Subtotal (95% CI)	**337**	**174**		**16.06%**	**1.31[0.65,2.62]**
Total events: 52 (Treatment), 20 (Control)					
Heterogeneity: Tau²=0.14; Chi²=3.06, df=2(P=0.22); I²=34.67%					
Test for overall effect: Z=0.75(P=0.45)					
3.12.6 Forgetfulness					
Jenike 1990b	1/10	0/9		0.83%	2.73[0.12,59.57]
Subtotal (95% CI)	**10**	**9**		**0.83%**	**2.73[0.12,59.57]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
3.12.7 Headache					
Chouinard 1990	5/43	7/44		4.81%	0.73[0.25,2.13]
Greist 1992b	92/241	22/84		10.96%	1.46[0.98,2.16]



Analysis 3.13. Comparison 3 SSRIs versus Placebo - adverse effects, Outcome 13 Sertraline - sexual side effects.



ADDITIONAL TABLES

Table 1. Critical appraisal of previous systematic reviews of treatment for OCD

Article	Focused question	Inclusion criteria	Comprehen search	Internal validity	Study assessment	Heterogeneity examin	Methods pooling data
QAP 1985	yes	not clear	reasonable	no	not clear	not clear	yes
Jenike 1990	yes	no	no	no	not clear	not clear	yes
Cox 1993	yes	no	reasonable	no	not clear	no	yes
van Balkom 1994	yes	no	yes	yes	yes	yes	yes (but not standardised
Greist 1995	yes	yes	no	no	not clear	yes	effect sizes compared only
Piccinelli 1995	yes	yes	reasonable	no	not clear	yes	yes
Stein 1995	yes	yes	reasonable	no	not clear	no	yes
Abramowitz 1996	yes	no	reasonable	no	no	no	yes
Abramowitz 1997	yes	yes	reasonable	no	no	no	yes
Kobak 1998	yes	for some comparisons	yes	yes	not clear	yes	yes
Christensen 1987	yes	yes	reasonable	only partial	yes	no	not clear
Ackerman 2002	yes	yes	yes	yes	not clear	yes	yes

WHAT'S NEW

Date	Event	Description
6 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 1, 2008

Date	Event	Description
10 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

G Mustafa Soomro: development of Background and Methods sections, study selection, data extraction, data analysis and writing up

D Altman: development of Methods section and data analysis

S Rajgopal: study selection and data extraction

M Oakley-Browne: development of Background and Methods sections

DECLARATIONS OF INTEREST

G Mustafa Soomro: None stated
D Altman: None stated
S Rajagopal: None stated
M Oakley-Browne: None stated

SOURCES OF SUPPORT

Internal sources

- St Georges Hospital Medical School, London SW17 0RE, UK.

External sources

- Systematic Reviews Training Unit, Institute of Child Health, London, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Obsessive-Compulsive Disorder [*drug therapy]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [*therapeutic use]

MeSH check words

Humans